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*American
Journal
of*

**OBSTETRICS
AND GYNECOLOGY**

TRANSACTIONS OF THE EIGHTY-THIRD ANNUAL MEETING
OF THE AMERICAN GYNECOLOGICAL SOCIETY

Editor in Chief

HOWARD C. TAYLOR, JR.

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Transactions of the Eighty-third Annual Meeting of the American Gynecological Society

Thomas Stephen Cullen. Presidential address <i>Karl H. Martzloff, M.D., Portland, Oregon</i>	833
Ovarian function following pelvic operation <i>Richard W. TeLinde, M.D., and Lawrence R. Wharton, Jr., M.D., Baltimore, Maryland</i>	844
Autopsy comparison of cardiovascular changes in castrated and normal women <i>Edmund R. Novak, M.D., and Tiffany J. Williams, M.D., Baltimore, Maryland</i>	863
Polycystic ovarian disease <i>Tommy N. Evans, M.D., and Gardner M. Riley, Ph.D., Ann Arbor, Michigan</i>	873
Metabolism of estrone-C ¹⁴ -16 sulfate in women <i>Gray H. Twombly, M.D., and Mortimer Levitz, Ph.D., New York, New York</i>	889
An experiment in the use of radioactive gold for cervical cancer <i>E. Stewart Taylor, M.D., N. Paul Isbell, M.D., and Robert E. Dean, M.D., Denver, Colorado</i>	899
Sodium cyanide as a cancer chemotherapeutic agent <i>Willis E. Brown, M.D., C. D. Wood, Ph.D., and A. N. Smith, B.S., Little Rock, Arkansas</i>	907
Distribution of metastases in Stage I carcinoma of the cervix <i>Erle Henriksen, M.D., Los Angeles, California</i>	919
Effects of pregnancy and labor on the breathing pattern of the newborn infant <i>Leroy A. Calkins, M.D., and Herbert C. Miller, M.D., Kansas City, Kansas</i>	933
Connective tissue changes incident to cervical effacement <i>D. N. Danforth, M.D., J. C. Buckingham, M.D., and J. W. Roddick, Jr., M.D., Chicago, Illinois</i>	939
Refractory anemias of pregnancy <i>Roy G. Holly, M.D., Omaha, Nebraska</i>	946

(Contents continued on page 2)

Contents continued from page 1

Blood volume changes in pregnancy and the puerperium. I. Does sequestration of red blood cells accompany parturition? <i>Jack A. Pritchard, M.D., Kenneth M. Wiggins, M.D., and John C. Dickey, M.D., Dallas, Texas</i>	956
Plasma nonesterified fatty acids in pregnancy. II. Experimental modification <i>Richard L. Burt, M.D., Winston-Salem, North Carolina</i>	965
End results in adenocarcinoma of the endometrium managed by preoperative irradiation <i>John B. Montgomery, M.D., Warren R. Lang, M.D., David M. Farrell, M.D., and George A. Hahn, M.D., Philadelphia, Pennsylvania</i>	972
Stage I carcinoma of the uterine cervix <i>Frank R. Lock, M.D., Frank C. Greiss, M.D., and Damon D. Blake, M.D., Winston-Salem, North Carolina</i>	984
Value of urologic study in the management of carcinoma of the cervix <i>Beaury C. Burns, Jr., M.D., Houston S. Everett, M.D., and C. Bernard Brack, M.D., Baltimore, Maryland</i>	997
Results of early repair of vesicovaginal fistula with preliminary cortisone treatment <i>Conrad G. Collins, M.D., and David Pent, M.D., New Orleans, Louisiana, and Frederick B. Jones, Mobile, Alabama</i>	1005
Detection of trophoblast in cord blood and fetal circulation <i>A. T. Salvaggio, M.D., G. Nigogosyan, M.D., and H. C. Mack, M.D., Detroit, Michigan</i>	1013

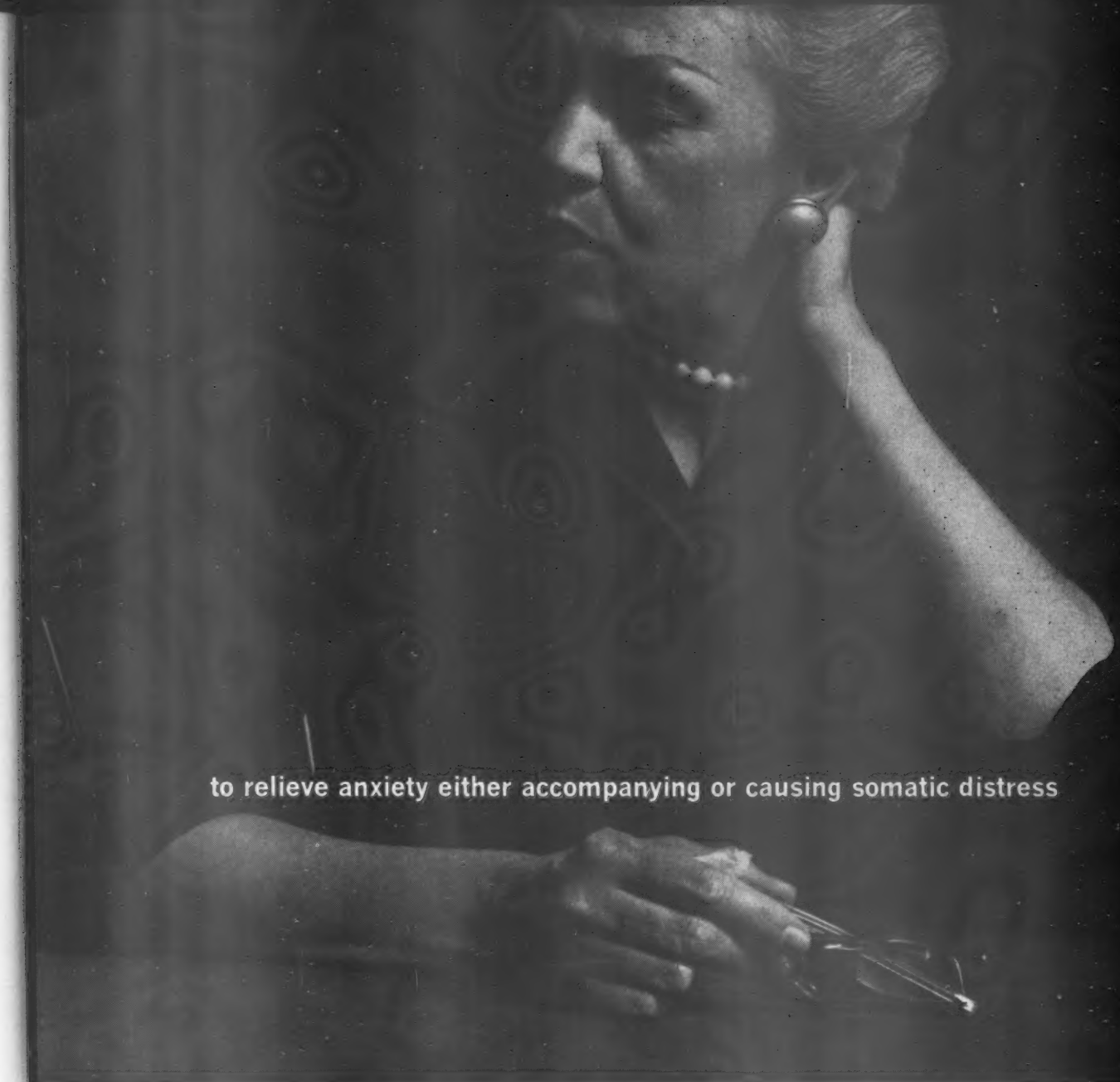
Department of current opinion

<i>Re-evaluation</i> Bruit placentaire <i>Rudolf G. Winkelbauer, Captain, MC, USA, and James E. Tatum, Captain, MC, USA, Stuttgart, Germany</i>	1022
Use of the intrauterine stem pessary <i>Ralph W. Eddy, M.D., and Juan C. Ruiz-Bueno, M.D., Cincinnati, Ohio</i>	1025

Reviews and abstracts

Selected abstracts	1031
--------------------	------

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1. Marx, F.J., in *Trifluoperazine: Further Clinical and Laboratory Studies*, Philadelphia, Lea & Febiger, 1959, p. 89.
2. Winkelman, N.W., Jr.: *ibid.*, p. 78.

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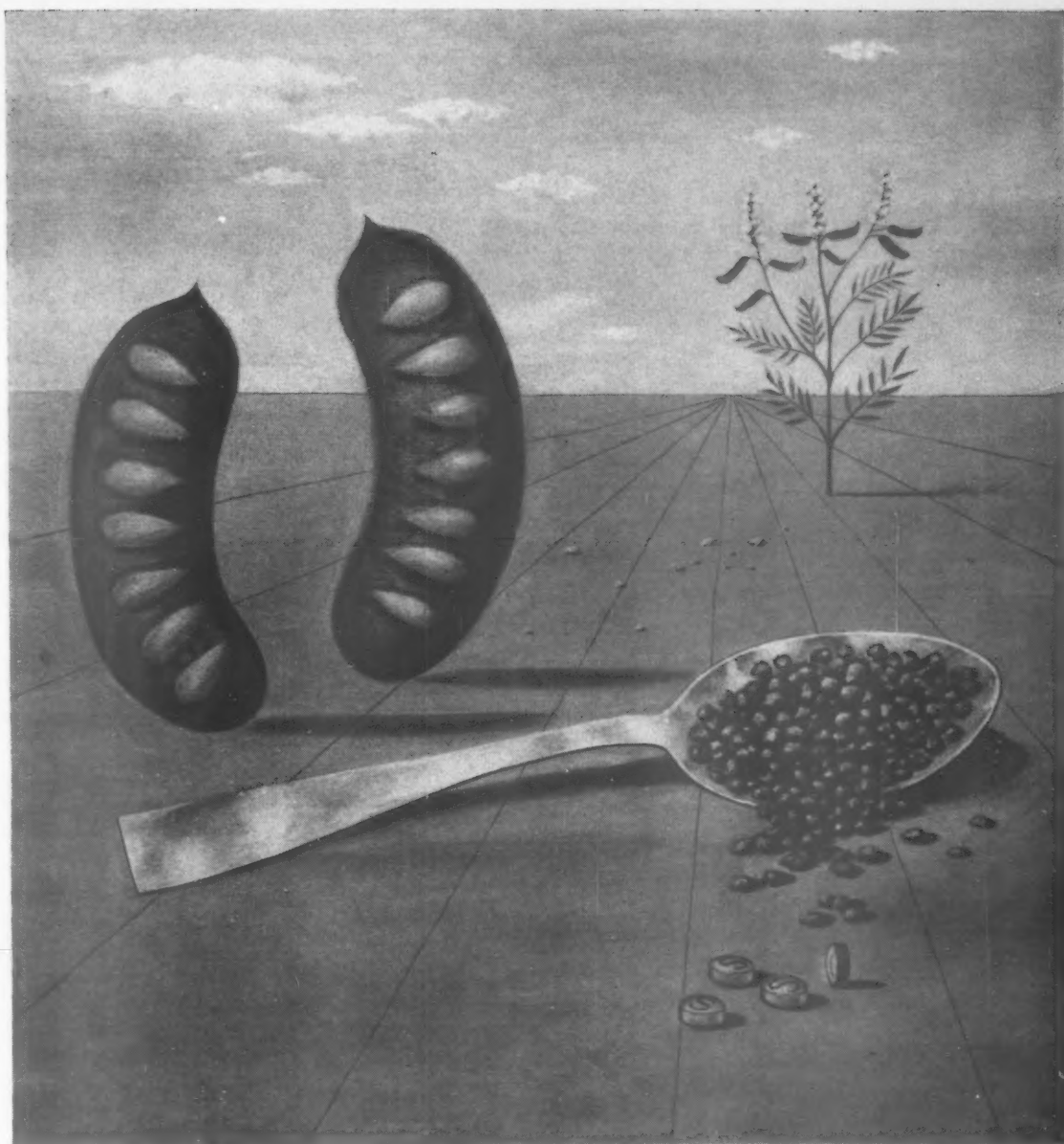
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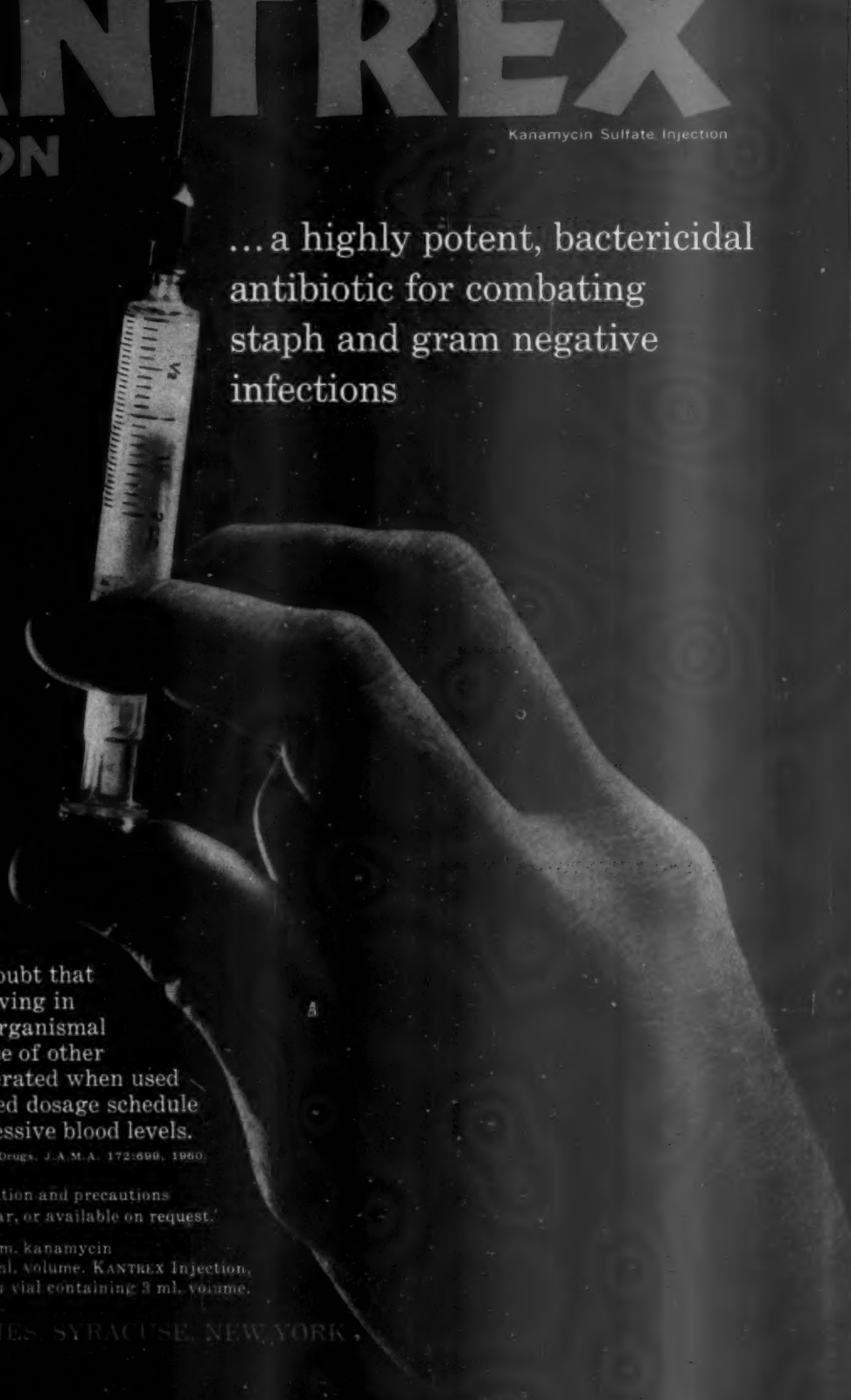
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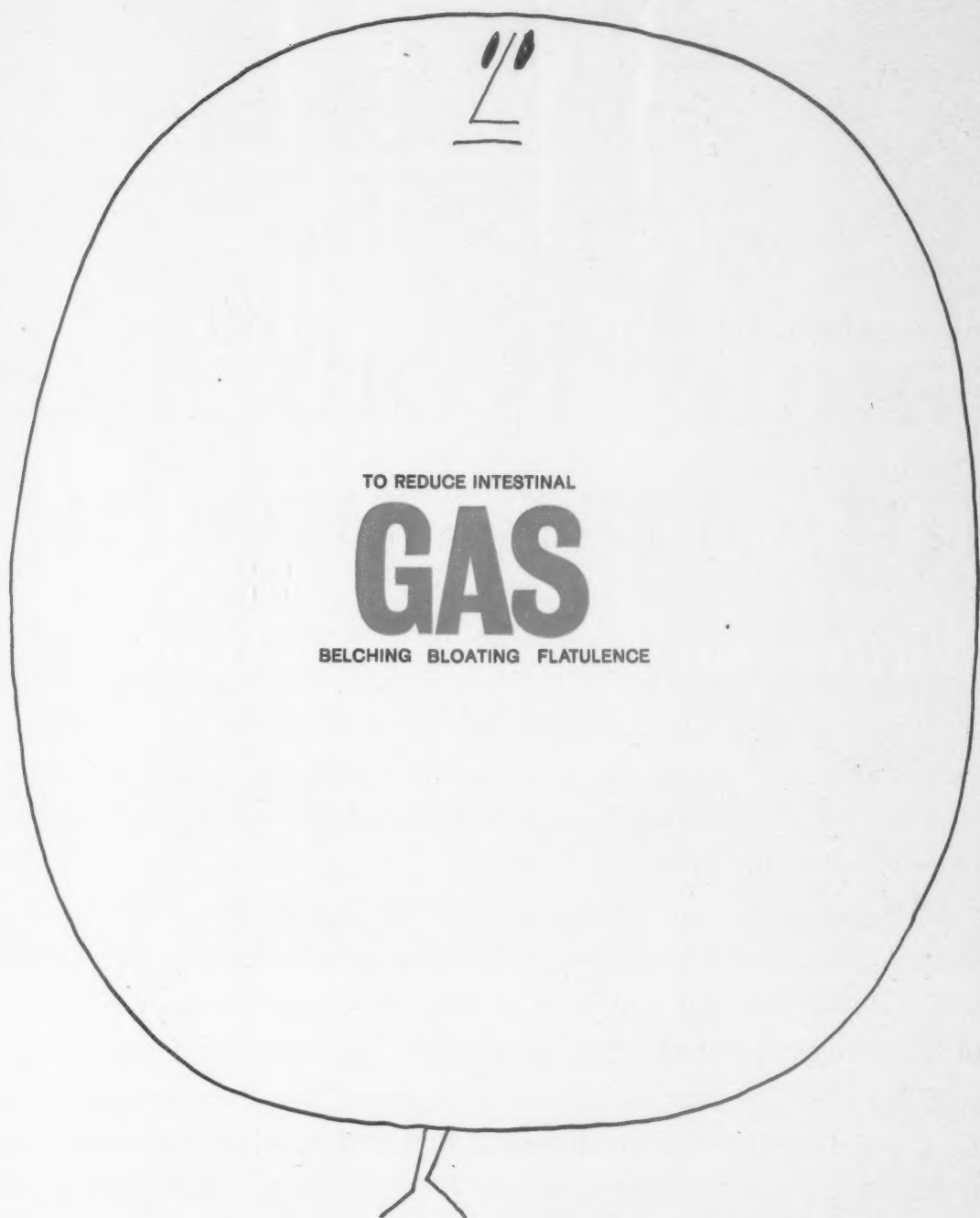
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1. Haden, R.L., Schneider, R.H., and Underwood, L.C.: Ann. N.Y. Acad. Sci., 49:641 (May 11, 1948).

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1. Derouaux, G., and Roskam, J.: Adrenaline, Adrenalone, and Mean Bleeding Time. *J. Physiol.* 90:65 (1937).
2. Roskam, J.: Arrest of Bleeding. Charles C. Thomas, Springfield, Ill. (1954).
3. Peels, J.C.: Adrenosem in the Control of Hemorrhage from the Nose and Throat. *A.M.A. Arch. of Otolaryng.* 61:450 (Apr., 1955).
4. Fulton, G.P., Lutz, B.R., Shulman, M.H., and Arendt, K.A.: Moccasin Venom as a Test for Susceptibility to Petechial Formation in the Hamster. Venoms: Published by the Am. Assoc. for the Advancement of Science (1954).
5. Pappenheimer, J.R.: Passage of Molecules Through Capillary Walls. *Physiol. Rev.* 33:387 (July, 1953).
6. Peels, J.C.: The Use of the Systemic Hemostat Carbazochrome Salicylate. *West. J. Surg., Obstet., and Gynec.* 64:86 (Jan., 1956).
7. Kingsbury, B.C., Jr., and Young, H.E.: A Preliminary Report on Adrenosem Salicylate for Control of Hemorrhage. *J. Calif. State Dental Assn. and Nev. State Dental Assn.* 31:53 (May-June, 1955).
8. Moss, A.A.: Control of Hemorrhage in Dental Surgery. *Dental Survey* 32:1622 (Dec., 1956).
9. Ryan, Allen J.: Control of Bleeding in Familial Telangiectasia. *The Meriden Hosp. Bull.* 7: (Jan., 1956).
10. Peels, J.C.: Further Observations on the Use of Adrenosem Salicylate in the Control of Hemorrhage from the Nose and Throat. *N. Car. Med. J.* 17:98 (Mar., 1956).
11. Peels, J.C.: Control of Hemorrhage from the Nose and Throat. *Med. Times* 86:1228 (Oct., 1958).
12. Brode, H.A., and Chianese, T.C.: A Clinical Evaluation of Adrenosem Salicylate. *Ann. of Dentistry* 15:56 (Sept., 1956).
13. Owings, Capers B.: The Control of Postoperative Bleeding with Adrenosem. *Laryngoscope* 65:21 (Jan., 1955).
14. Perkins, R.E.L.: A Clinical Investigation of Adrenochrome Monosuccinylcarbazone Sodium Salicylate. *Oral Surg., Oral Med., Oral Path.* 10:230 (Mar., 1957).
15. Zubieta, C.B., and Escanverino, R.F.: Adrenosem for the Prevention of Bleeding in Tonsillectomy. *Am. Pract. & Dig. of Treatment* 8:355 (Mar., 1957).
16. Orzic, E.: Medical Care of the Child Patient Before and After Adenoidectomy and Tonsillectomy. *N.Y. State J. Med.* 56:884 (Mar., 1956).
17. Fiddle, A.C., Jr.: Adrenosem Salicylate: A Systemic Hemostatic. *Oral Surg., Oral Med., Oral Path.* 8:617 (June, 1955).
18. Roberts, E.W.: Observations on the Use of Adrenochrome in Dental Practice. *Oral Surg., Oral Med., Oral Path.* 10:52 (Jan., 1957).
19. Brown, W.S.: Control of Bleeding After Dermabrasion. *Northwest Med.* 57:470 (Apr., 1956).
20. Dimmette, J.E., and Terry, J.G.: Better Control of Bleeding in Vaginal Hysterectomy, presented before the Texas State Med. Society, Surgical Section (Jan., 1956).
21. Sherber, D.A.: The Control of Bleeding. *Am. J. Surg.* 65:331 (Sept., 1953).
22. Dennehy, P.J.: The Care of the Prostatic Cavity. *S. African Med. J.* 50:381 (Apr., 1956).
23. Ersner, M.S., and Lerner, S.B.: The Unsolved Problem of the Tonsils and Adenoids. *The Med. Clinics of N. Amer.* 40:1749 (Nov., 1956).
24. Reel, H.B.: Minimizing Postoperative Ecchymosis. *The J. of Surgery* 96:781 (Dec., 1958).
25. Coyle, J.E.: Analysis of Blood and Vascular Factors in the Prophylaxis of Tonsillo-Adenoidal Hemorrhage. *Laryngoscope* 10:1029 (Oct., 1957).
26. Proctor, D.F., and Douglass, C.C.: Bleeding Following Tonsil and Adenoid Operations. *Trans. Amer. Acad. Ophthalm. Otolaryngol.* 62:592 (July-Aug., 1958).
27. Bourgoynne, J.R.: Adrenosem and the Bleeder (in press).
28. Nicely, P., F.A.C.S., F.I.C.S. (Personal communication).
29. Wilkins, B.D.: Gastrointestinal Bleeding as Seen by the Proctologist. *J.A.M.A.* 153:1214 (April 6, 1957).
30. Feinblatt, T.M., Feinblatt, H.M., and Ferguson, E.A.: Successful Non-Surgical Uses of Carbazochrome Salicylate. *Amer. Pract. & Dig. of Treatment* 9:1827 (Nov., 1958).
31. Stich, M.H.: Carbazochrome Salicylate Therapy in Hereditary Hemorrhagic Telangiectasia. *N.Y. State J. of Med.* 59:2725 (July 15, 1959).

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References:

(1) Stenger, E. G., et al.: Schweiz. med. Wchnschr.
89:1126, 1959. (2) Fuchs, M., Res: et al.: Current
Therap. Research 2:11, January, 1960. (3)
Ford, R. V.: Manuscript submitted for publication.



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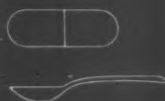
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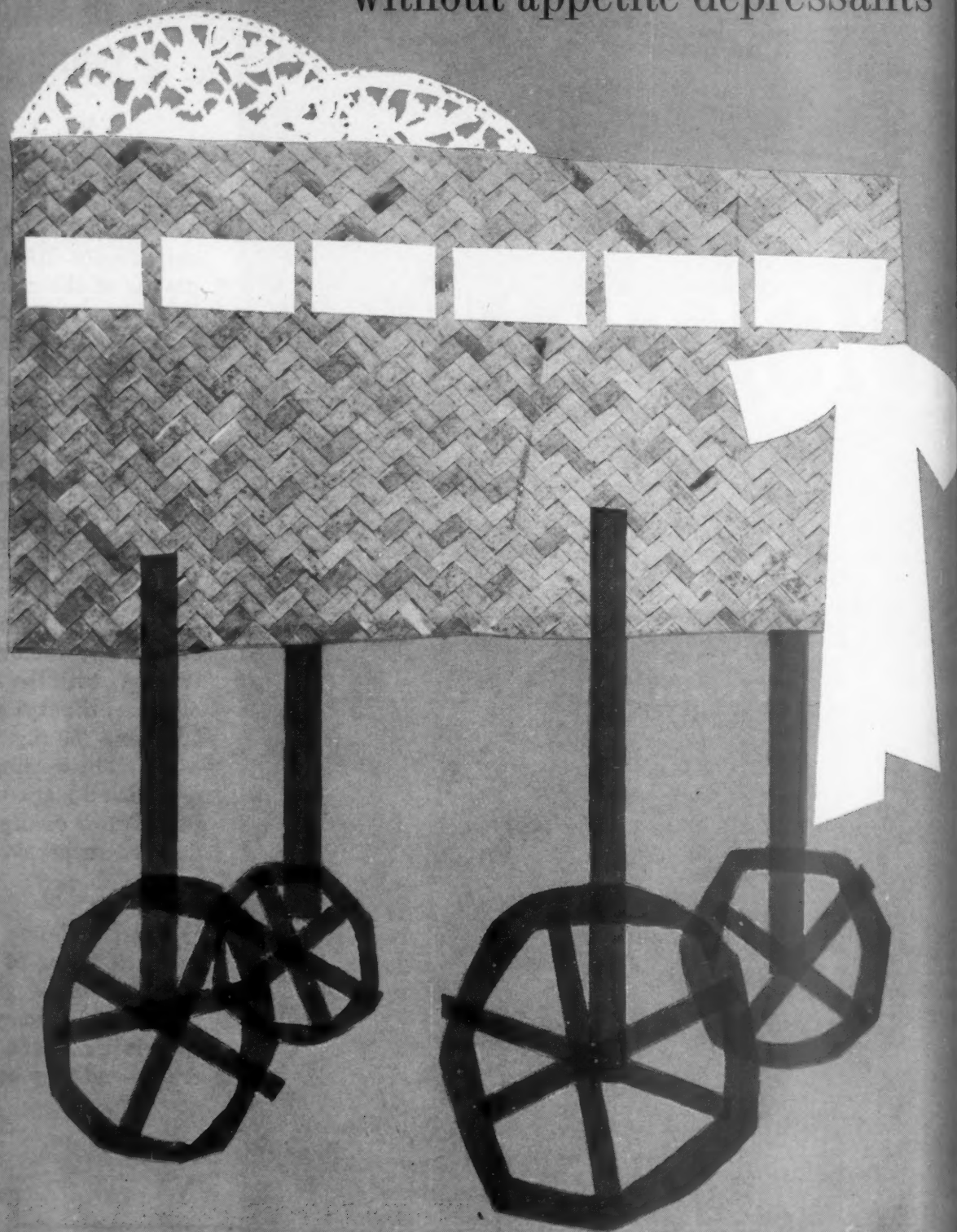
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- (1) Antos, R. J.: The Use of a New Dietary Product (Metrecal) For Weight Reduction, *Southwestern Med.* 40:695-697 (Nov.) 1959. (2) Tullis, I. E.: Initial Experience with a Simple Weight Control Formula, to be published.
- (3) Roberts, H. J.: Effective Long-Term Weight Reduction—Experiences with Metrecal, to be published.



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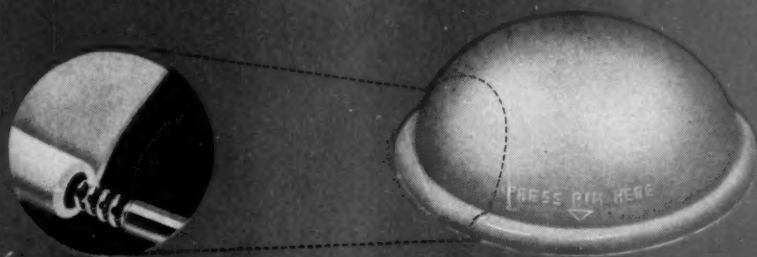
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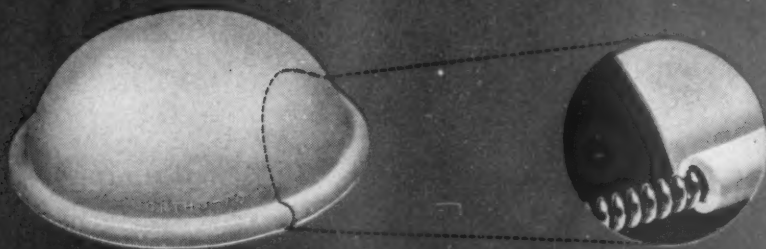
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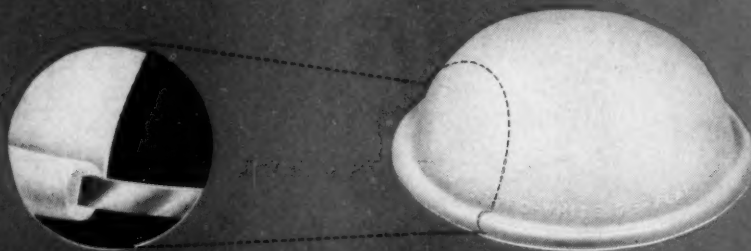
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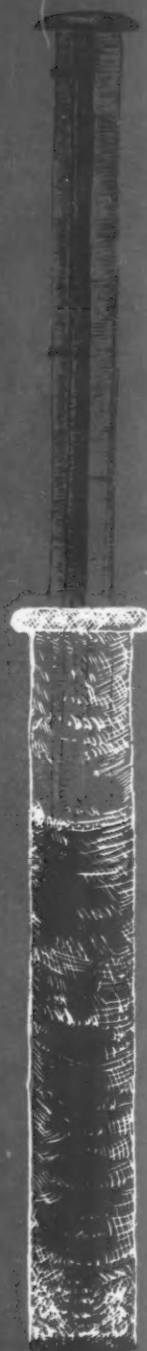
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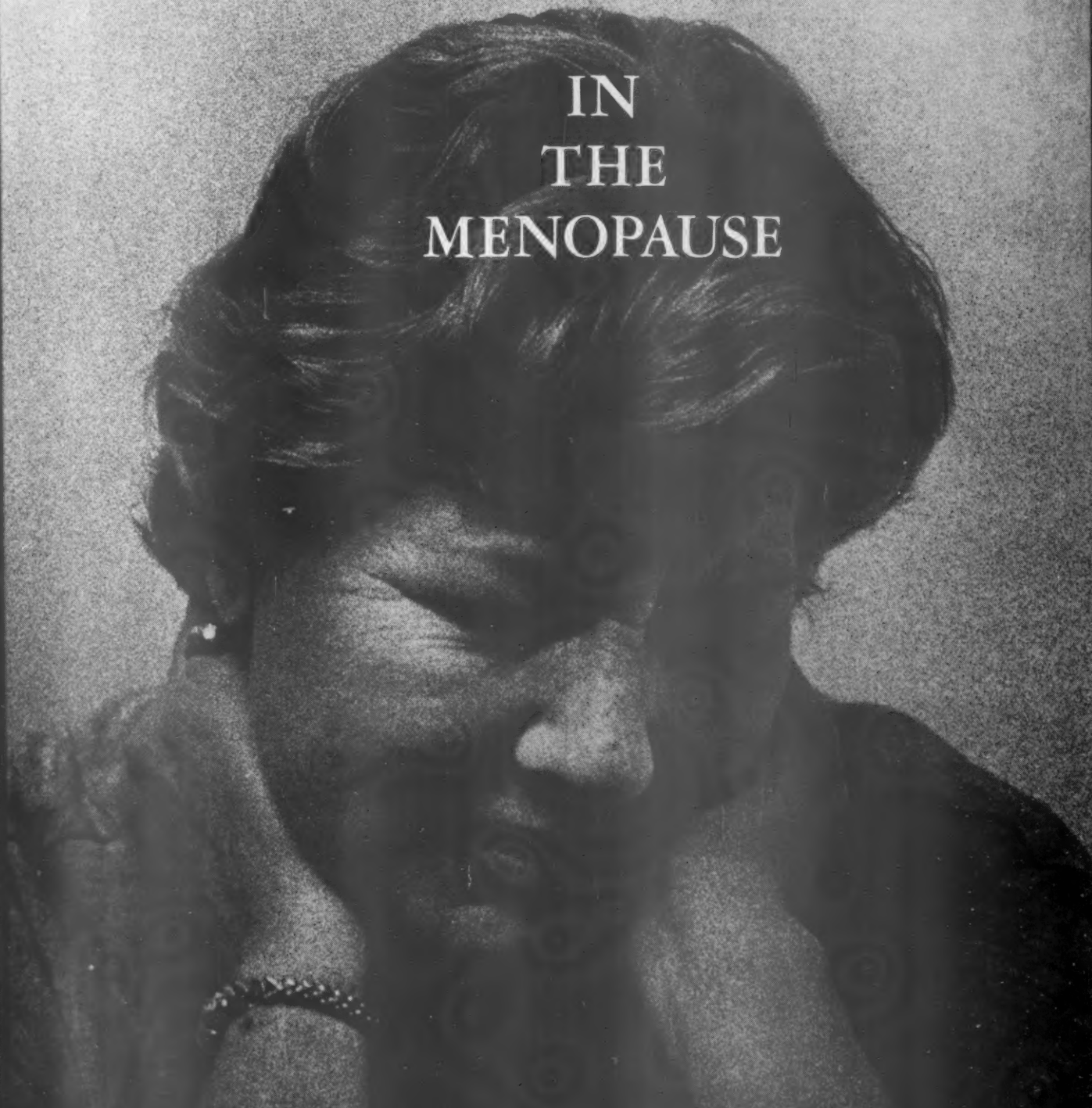
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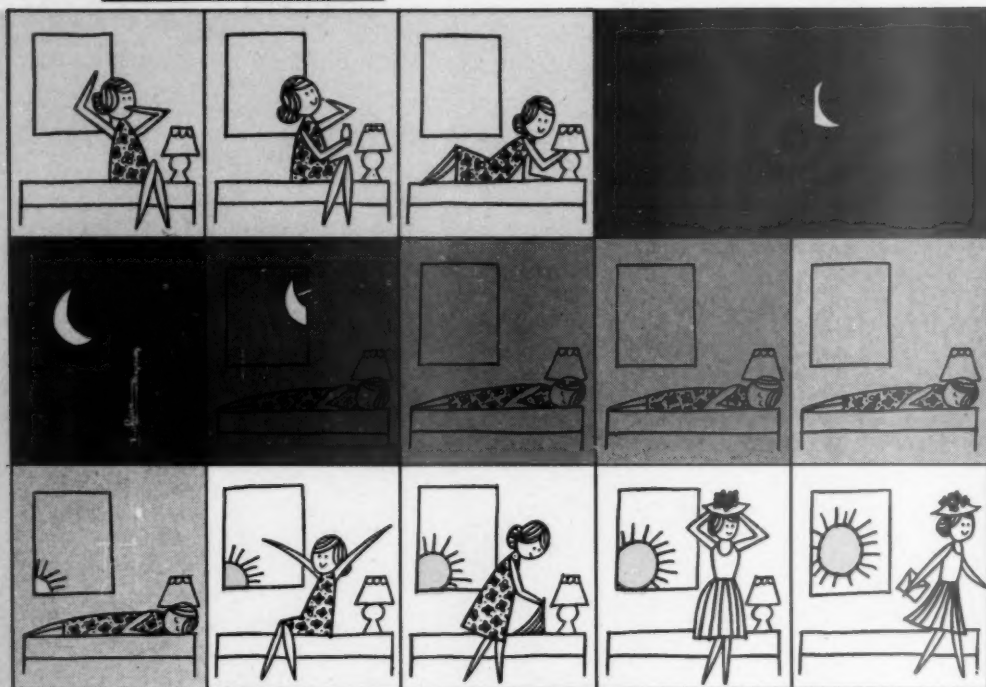
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Medication	Number of patients	Complete relief	Partial relief	Failure
Bendectin	52	23 (44%)	26 (50%)	3 (6%)
		TOTAL 94%		
Placebo	57	13 (23%)	24 (42%)	20 (35%)
		TOTAL 65%		

"Bendectin was administered in a preliminary study to 146 patients and later, in a controlled, double-blind study to 52 patients, or to a total of 198 patients suffering from nausea and vomiting of pregnancy. A very gratifying therapeutic response was obtained in 178 or 90 per cent. In a double-blind portion of this study, the response of 52 patients treated with Bendectin was compared with that of 57 other patients treated with a placebo. In this group of 109 patients, there was a favorable response to Bendectin in 94 per cent and to the placebo in only 65 per cent."²

Measure Bendectin against your present Rx:

Q. Has your present Rx been shown to relieve morning sickness — before it starts — in more than 9 out of 10 patients?²⁻⁵

Q. Is your present Rx free of phenothiazine-like side effects and habituating properties?

Q. Is it economical? Does it cost less per day, for example, than a quart of milk?

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Each white, specially coated tablet contains:
Bentyl (dicyclomine) hydrochloride 10 mg.
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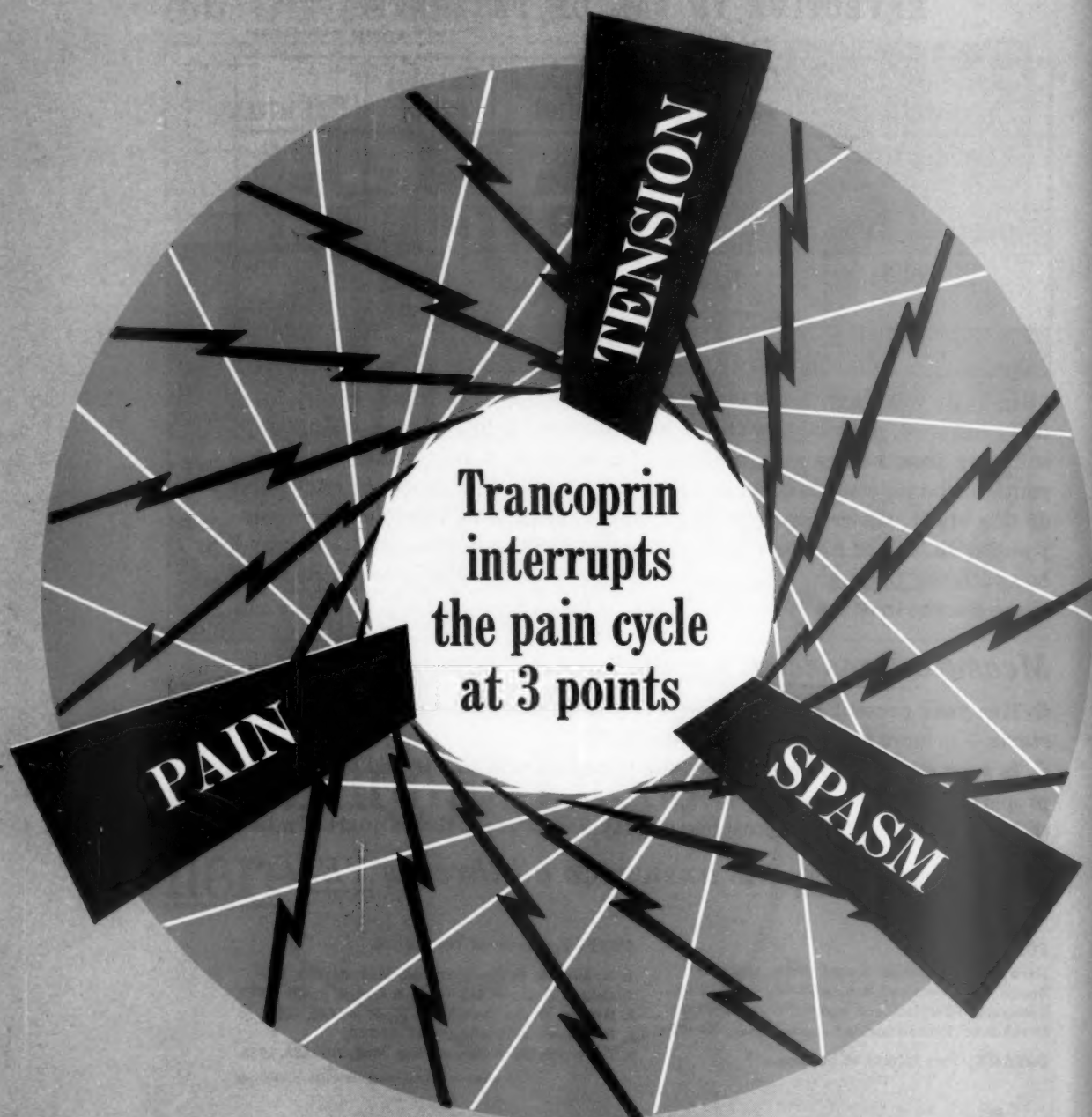
SUPPLY: Bottles of 100 and 500.

1. Middleton, T. F.: Postgrad. Med. 24:699, 1958.
2. Geiger, C. J., et al.: Obst. & Gynec. 5:688, 1959.
3. Nulsen, R. O.: Ohio State M. J. 53:665, 1957.
4. Personal communications, 1956-57.
5. Towne, J. E.: Internat. Rec. Med. 171:583, 1958.

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Exceptionally Safe

No serious side effects have been encountered with Trancoprin. Of 923 patients treated with Trancoprin, only 22 (2.4 per cent) experienced any side effects.^{8,9} In every instance, these reactions, which included temporary gastric distress, weakness or sedation, were mild and easily reversed.

Indications

Trancoprin is recommended for more comprehensive control of the pain complex (pain → tension → spasm) in those disorders in which tension and spasm are complicating factors, such as: headaches, including tension headaches / premenstrual tension and dysmenorrhea / low back pain, sciatica, lumbago / musculoskeletal pain associated with strains or sprains, myositis, fibrositis, bursitis, trauma, disc syndrome and myalgia / arthritis (rheumatoid or hypertrophic) / torticollis / neuralgia.

Dosage

The usual adult dosage is 2 Trancoprin tablets three or four times daily. The dosage for children from 5 to 12 years of age is 1 tablet three or four times daily. Trancoprin is so well tolerated that it may be taken on an empty stomach for quickest effect. The relief of symptoms is apparent in from fifteen to thirty minutes after administration and may last up to six hours or longer.

How Supplied

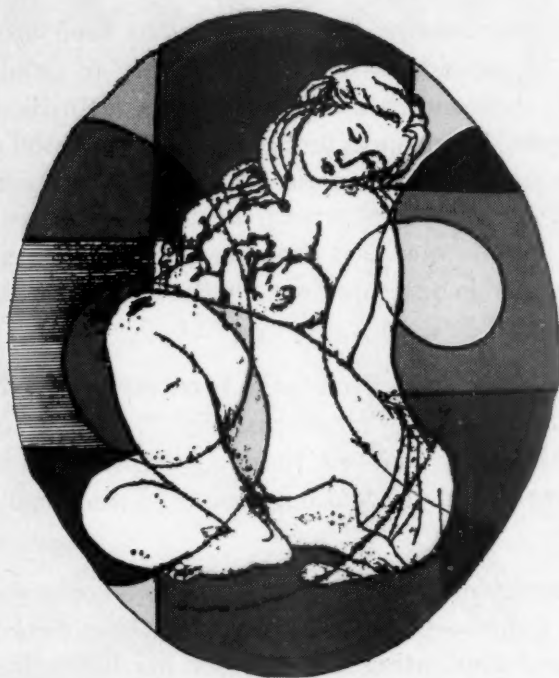
Each Trancoprin tablet contains 300 mg. (5 grains) of acetylsalicylic acid and 50 mg. of chlormezanone [Trancopal® brand]. Bottles of 100 and 1000.

Trancoprin Tablets / non-narcotic analgesic

References: 1. DeNyse, D. L.: *M. Times* 87:1512, Nov., 1959. 2. Ganz, S. E.: *J. Indiana M. A.* 52:1134, July, 1959. 3. Gruenberg, Friedrich: *Current Therap. Res.* 2:1, Jan., 1960. 4. Kearney, R. D.: *Current Therap. Res.* 2:127, April, 1960. 5. Lichtman, A. L.: *Kentucky Acad. Gen. Pract. J.* 4:28, Oct., 1958. 6. Mullin, W. G., and Epifano, Leonard: *Am. Pract. & Digest Treat.* 10:1743, Oct., 1959. 7. Shanaphy, J. F.: *Current Therap. Res.* 1:59, Oct., 1959. 8. Collective Study, Department of Medical Research, Winthrop Laboratories. 9. Hergesheimer, L. H.: An evaluation of a muscle relaxant (Trancopal) alone and with aspirin (Trancoprin) in an industrial medical practice, *Ibid.*

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1. Macy, I. G.; Kelly, H. J., and Sloan, R. E.; with the Consultation of the Committee on Maternal and Child Feeding of the Food and Nutrition Board, National Research Council: The Composition of Milks, Publication 254, National Academy of Sciences and National Research Council, Revised 1953. 2. Brown, G. W.; Tuholski, J. M.; Sauer, L. W.; Minsk, L. D., and Rosenstern, I.: Evaluation of Prepared Milks in Infant Nutrition; Use of the Latin Square Technique, J. Pediatr. 56:391 (Mar.) 1960.



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See over for therapy in difficult patients ►

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RECORD OF SAFETY

In clinical studies of over 3,600 patients, the number of reactions, none serious, was less than 2 per cent.¹⁻⁶ "Thiosulfil" was remarkably well tolerated, there being no discontinuation of treatment due to untoward effects, and very few mild reactions were noted."² "The drug can be taken over a long period of time with practically no untoward side reactions."³ "Clinical trial appears to indicate that the drug can be tolerated where other sulfa drugs cannot and that it is effective where some others are not."⁴ Out of 3,057 cases . . . 47 patients (1.6%) showed g.i. disturbances and 33 patients (1.1%) allergic reactions.¹ NO REPORTS OF: hemorrhagic dyscrasias, hematuria, anuria, agranulocytosis.

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A review of more than 3,600 reported cases on "Thiosulfil" demonstrates: a) adequate drug dosage can be simply and economically achieved with a minimum incidence of complicating side effects; b) the antibacterial agent can be given over longer periods of time, particularly in cases involving urinary stasis.

Specific For Urinary Tract Infections: "Thiosulfil" reaches greater urinary concentrations in the active, free, nonmetabolized form than any other sulfa, single or mixed. "Thiosulfil" is rapidly excreted; as much as 79% of the drug is found in the urine after eight hours—of this, 98% is in the active form.⁵ The entire g.u. tract is, thus, subjected to continual "sulfa baths" of active drug—more wide spectrum antibacterial activity at site of infection.

Even where urinary stasis exists and cannot be readily corrected, prolonged or even indefinite use of "Thiosulfil" on a reduced dosage schedule will usually keep the infection under control, patients comfortable, and side effects minimal. "Thiosulfil" may materially reduce the likelihood of infections ascending to the parenchyma of the kidneys and subsequent serious systemic involvement.

DOSAGE (Urinary Tract Infections)

TIME PERIOD	DOSE
First two weeks	3 Gm./day ¹
2 weeks to 3 months	2 Gm./day ^{2, 6}
3 months or longer	0.5 Gm./day ⁷

Suggested Range of Dosage: 1 or 2 tablets three or four times daily. **Note:** The usual precautions exercised with sulfonamides should be observed.

Supplied: No. 786: Each tablet contains 0.5 Gm. sulfamethizole; in bottles of 100 and 1,000 scored tablets.

References—1. Bourque, J.-P., and Gauthier, G.-E.: Seven years' experience with sulfamethizole, to be published. 2. Bourque, J.-P., and Joyal, J.: Canad. M.A.J. 68:337 (Apr.) 1953. 3. Barnes, R. W.: J. Urol. 71:655 (May) 1954. 4. Goodhope, C. D.: J. Urol. 72:552 (Sept.) 1954. 5. Boger, W. P.: The Antibacterial Sulfonamides: Comparative Studies, Scientific Exhibit Section, American Academy of General Practice Eleventh Annual Scientific Assembly, Apr. 6-9, 1959, San Francisco, California. 6. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: Rocky Mountain M. J. 56:66 (Mar.) 1959. 7. Hughes, J., Coppridge, W. M., and Roberts, L. C.: North Carolina M. J. 17:320 (July) 1956.

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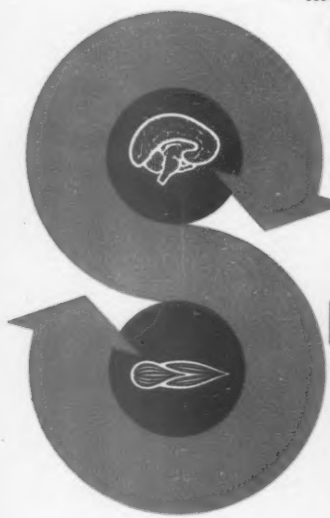
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- much less drowsiness than with meprobamate, phenothiazines, or the psychosedatives
- does not impair intellect, skilled performance, or normal behavior
- neither depression nor significant toxicity has been reported

 **Striatran** [®] *alert tranquillity*
EMYLCAMATE

- a familiar spectrum of antianxiety and muscle-relaxant activity
- no new or unusual effects—such as ataxia or excessive weight gain
- may be used in full therapeutic dosage even in geriatric or debilitated patients
- no cumulative effect
- simple, uncomplicated dosage, providing a wide margin of safety for office use

STRIATRAN is indicated in anxiety and tension, occurring alone or in association with a variety of clinical conditions.

Adult Dosage: One tablet three times daily, preferably just before meals. In insomnia due to emotional tension, an additional tablet at bedtime usually affords sufficient relaxation to permit natural sleep.

Supply: 200 mg. tablets, coated pink, bottles of 100.

While no absolute contraindications have been found for Striatran in full recommended dosage, the usual precautions and observations for new drugs are advised.

For additional information, write Professional Services,
Merck Sharp & Dohme, West Point, Pa.



MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

STRIATRAN IS A TRADEMARK OF MERCK & CO., INC.



**SAFE
AND
SOUND**
IN ANY PREGNANCY

to prevent morning sickness

With new Tigan 250 mg capsules you can now provide protection against morning sickness with only two capsules daily — one at bedtime and one in the morning. Tigan is so safe that it may be used with confidence as a routine prescription in any pregnancy. Avoiding the risks of phenothiazine derivatives and the limitations of the antihistamines, Tigan acts both therapeutically and prophylactically to stop active vomiting or to prevent nausea and vomiting.

Consult literature and dosage information, available on request, before prescribing.

TIGAN BIBLIOGRAPHY: 1. M. W. Goldberg, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 2. O. C. Brandman, *ibid.* 3. J. A. Lucinian and R. H. Bohn, *ibid.* 4. D. W. Molander, *ibid.* 5. B. I. Shnider and G. L. Gold, *ibid.* 6. W. S. Derrick, *ibid.* 7. B. Wolfson and F. F. Foldes, *ibid.* 8. L. McLaughlin, *ibid.* 9. W. K. Gauthier, Discussant, *ibid.* 10. H. E. Davis, Discussant, *ibid.* 11. I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, *J. Newark Beth Israel Hosp.*, 9:189, 1958. 12. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, *J. Pharmacol. & Exper. Therap.*, 126:270, 1959. 13. W. B. Abrams, I. Roseff, J. Kaufman, L. M. Goldman and A. Bernstein, *New York J. Med.*, 59:4217, 1959. 14. O. W. Doyle, *Clin. Med.*, 7:43, 1960. 15. L. A. Nathan, *Curr. Therap. Res.*, 2:6, 1960. 16. Council on Drugs, New and Nonofficial Drugs, *J.A.M.A.*, 172:1038, 1960. 17. O. L. Davidson, *J. Tennessee M.A.*, 53:140, 1960. 18. O. Brandman, *Gastroenterology*, 38:777, 1960. 19. B. A. Robin, *Maryland M. J.*, in press. 20. A. L. Kolodny, *Am. J. M. Sc.*, 239:682, 1960. 21. F. Cacace, *Colorado GP*, 2:5, 1960. 22. J. W. Bellville, I. D. J. Bross and W. S. Howland, *Clin. Pharmacol. & Therap.*, in press.

TIGAN® Hydrochloride—4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl) benzylamine hydrochloride



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Tigan

NEW 250 mg CAPSULES

for faster, more prolonged, more effective antiemetic activity



When
there's
a pram
in her
future,

What a happy reflection she sees! Any wonder, on such an occasion? However, long before that new maternity outfit became appropriate, a good prenatal supplement would have probably been in order. This is where Pramilets fill the bill. With just a single Filmtab daily, Pramilets provide twenty essential vitamins and minerals, including an ample dosage of phosphorus-free calcium and iron, in the form of well-tolerated ferrous fumarate. (And, speaking of Filmtab, the advantages of this exclusive Abbott coating are in evidence here, too: A compact tablet... freedom from those objectionable vitamin tastes or odors... a bright, baby-pink, calorie-free coating... tablets that won't chip or stick in the bottle... and increased protection against loss of potency.) That name, again? Pramilets. For the lady with a pram in her future.

she'll
need
Pramilets®

Comprehensive vitamin-mineral support with just one Filmtab daily.



Pramilets—Abbott's Phosphorus-free Prenatal Supplement.
Filmtab—Film-sealed Tablets, Abbott; U.S. Pat. No. 2,881,065.



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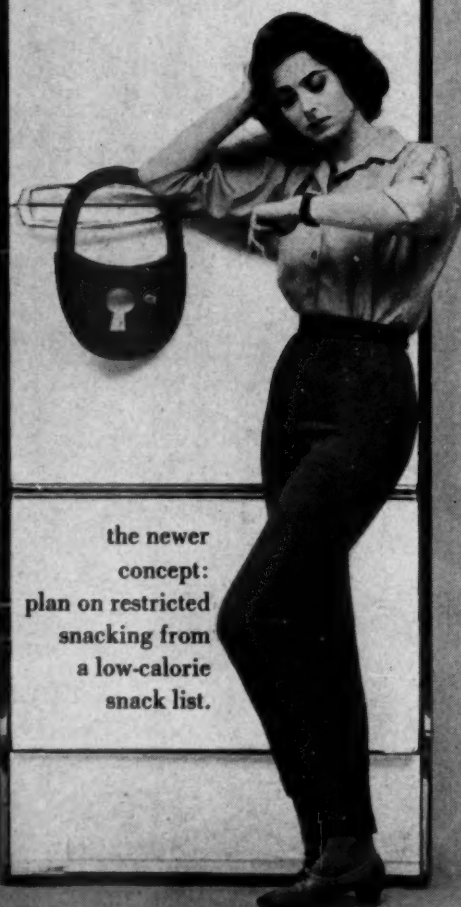
today



IF YOUR
OVERWEIGHT
PATIENTS
CHEAT
ON THEIR
DIETS
—HELP THEM



Most people
cheat on
their diets



the newer
concept:
plan on restricted
snacking from
a low-calorie
snack list.

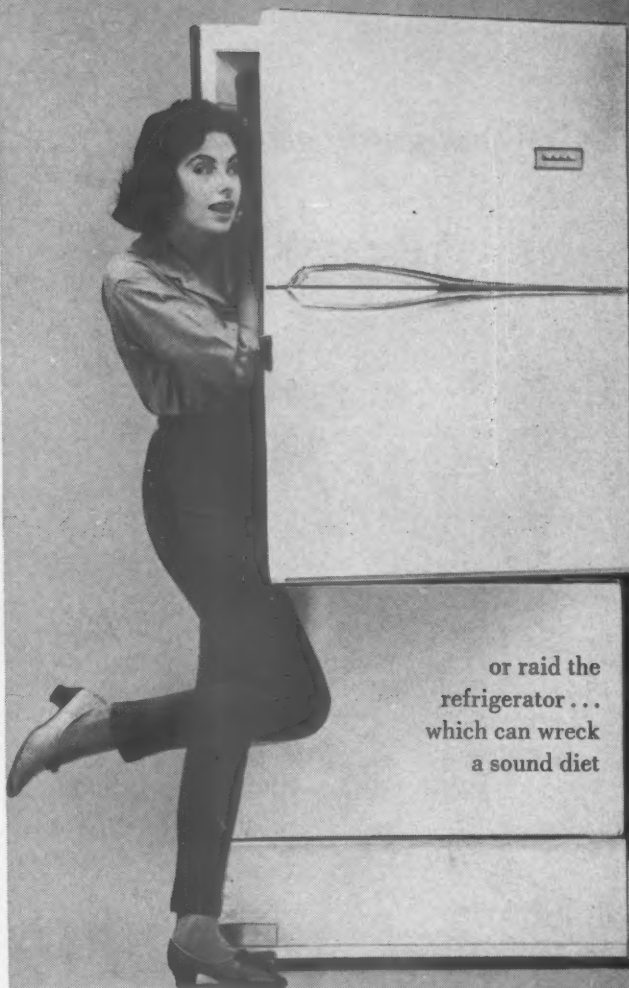


Before meals
or at bedtime . . .



or skip meals,
now and again

3



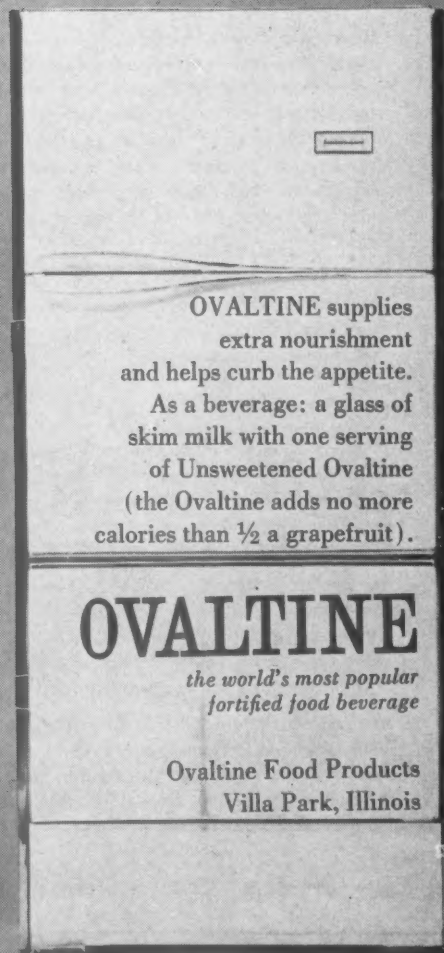
or raid the
refrigerator...
which can wreck
a sound diet

4



...snack with
Ovaltine

7



OVALTINE supplies
extra nourishment
and helps curb the appetite.
As a beverage: a glass of
skim milk with one serving
of Unsweetened Ovaltine
(the Ovaltine adds no more
calories than $\frac{1}{2}$ a grapefruit).

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*the world's most popular
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8

"comprehensive" multivitamins—friend or foe?



Although not itself harmful, the small amounts of folic acid in "comprehensive" multivitamins can correct significant blood disorders to confuse the diagnosis and delay the treatment of pernicious anemia victims.¹⁻¹³ Peripheral blood and bone marrow data may appear normal¹ in such patients while accompanying nerve degeneration continues. Diagnosis delayed by normal appearing indices can thus allow irreparable neurologic damage to occur before the true nature of the disease is recognized and treatment begun.⁴

To help physicians avoid this threat, Robins has formulated Adabee®, a new therapeutic multivitamin without folic acid, that is especially safe for long-term nutritional therapy in patients who require maximum support.

why no vitamin B₁₂ in Adabee®?

In order to obtain therapeutic levels of specific vitamins for certain individual deficiencies, doctors must often employ a "comprehensive" multivitamin.^{4,7} Many such elongated formulas include as ingredients substances which are nonessential, expensive to the patient, and irrational.^{4,7,10}

On the basis that B₁₂ in therapeutic vitamin mixtures has been described as needless by the A. M. A.,² and its unnecessary^{8,10,14,15} and indiscriminate use¹ has been criticized by astute hematologists,⁷ internists,¹⁰ pathologists,^{12,13} and nutritional workers,³ this member of the B-complex has also been omitted from Adabee.

In a rational formula,^{2,4,16,17} the need for hormones, enzymes, amino acids, or yeast is not supported. And since these superfluous substances might encumber the desired response to concurrently administered drugs, they are not found in the Adabee formulas.

Each yellow, capsule-shaped Adabee® tablet contains:

Vitamin A	25,000 USP units
Vitamin D	1,000 USP units
Thiamine mononitrate (B ₁)	15 mg.
Riboflavin (B ₂)	10 mg.
Pyridoxine HCl (B ₆)	5 mg.
Nicotinamide (niacinamide)	50 mg.
Calcium pantothenate	10 mg.
Ascorbic acid (vitamin C)	250 mg.

Each green, capsule-shaped Adabee®-M tablet contains Adabee, plus nine minerals:

Iron	15.0 mg.
Iodine	0.15 mg.
Copper	1.0 mg.
Manganese	1.0 mg.
Magnesium	6.0 mg.
Zinc	1.5 mg.
Potassium	5.0 mg.
Calcium	103.0 mg.
Phosphorus	80.0 mg.

references:

1. Ellison, A. B. C., J.A.M.A., 173:240, 1960.
2. White, P. L., Sec'y, A.M.A. Council on Foods and Nutrition, J.A.M.A., 169:41, 1959.
3. New Eng. J. M., Vol. 259, No. 23, Dec. 18, 1958, p. 1231.
4. Goodman, L. S., and Gilman, A., *The Pharmacological Basis of Therapeutics*, 2nd ed., New York, Macmillan, 1955, pp. 1709-10, 1489-91.
5. *Federal Register*, Vol. 25, No. 136, July 14, 1960, p. 6633.
6. Conley, C. L., and Krevans, J. R., New Eng. J. M., 245:529-31, 1951.
7. Wintrobe, M. M., *Clinical Hematology*, 3rd ed., Phila., Lea & Febiger, 1952, pp. 398-400.
8. Frohlich, E. D., New Eng. J. M., 259:1221, 1958.
9. Vilter, R. W., *Modern Medicine*, 23:15, p. 90, Aug. 1960.
10. Bean, W. B., *Drugs of Choice: 1960-61*, W. Modell, ed., St. Louis, C. V. Mosby Co., 1960, pp. 115-16.
11. Crosby, W. H., Col., M.C., U.S.A., *Military Medicine*, 125:233, April, 1960.
12. Harris, C. E. C., Conn. State Med. J., pp. 543-45, July 1958.
13. Todd, Sanford, and Wells, *Clinical Diagnosis By Laboratory Methods*, 12th ed., W. B. Saunders, Phila., 1954, pp. 306-7.
14. Goldsmith, G. A., Am. J. of M., 25:680, Nov. 1958.
15. Darby, W. J., Am. J. of M., 25:726, Nov. 1958.
16. *GP*, Vol. XVIII, No. 2, p. 119, Aug. 1958.
17. J.A.M.A., Vol. 173, No. 16, pp. 1831-32, 1960.

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*for excellent protein
utilization
& easy iron
assimilation*

*for excellent utilization
of protein and calories*

MODILAC *a new prepared milk formula with nutritional & flavor advantages*

Modilac provides excellent protein and calorie utilization. A recent clinical study* demonstrated that infants receiving Modilac, in general, performed more efficiently than those of the control groups; weight increment from 2 to 16 weeks was highest; weight gain *per unit* of protein or *per calorie* was greatest.

Looks like milk... tastes like milk. Modilac is prepared by a special "flash-sterilization" process. Caramelization and browning, the results of prolonged high temperatures and amino-sugar bonding, are markedly reduced. It also reduces the destruction of heat-labile amino acids and vitamins to a new minimum.

The carbohydrate modifier in Modilac combines dextrans (76%) maltose and dextrose in proper proportion for "spaced CHO assimilation." This results in more uniform blood sugar levels and minimizes fermentation in the gastrointestinal tract.

Corn oil, which replaces butterfat, reduces intake of saturated fatty acids. Added vitamins A, C, D, B₆ and thiamine appropriately supplement the natural vitamin content. See back of insert for analysis.

*Luis L. Mosovich, M.D., Vivian Pessin, M.A., and Charles U. Lowe, M.D. (University of Buffalo and Buffalo Children's Hospital), PROGRAM AND ABSTRACTS, American Pediatric Society, 70th Annual Meeting, May, 1960.



*for easy iron
assimilation*

Gerber baby

CEREALS

*specially prepared to provide
extra nutritional advantages*

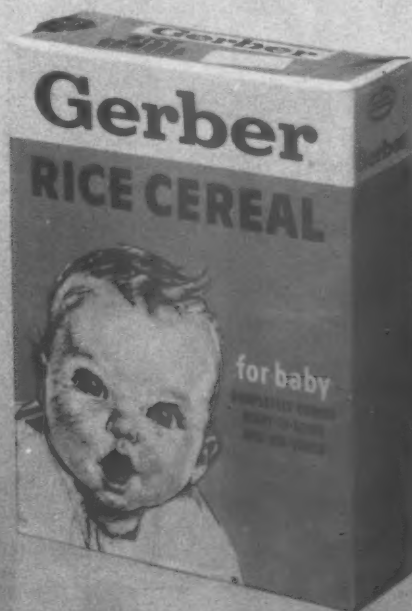
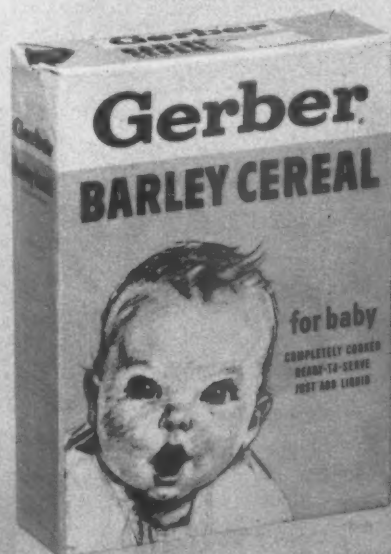
Gerber Cereals are prepared from an exclusive cereal formulation which includes a selected form of iron (sodium iron pyrophosphate) which is as easily absorbed and to the same degree as the iron found in natural sources.¹ One-half ounce (6 tablespoons) of any Gerber Cereal supplies 7 mg. iron...100% of the Recommended Daily Dietary Allowance for infants.²

Additional nutritional benefits: added thiamine, riboflavin and niacin supplement the vitamin content of the cereal and that of the infant's formula. See next page for analysis.

Easy assimilation is assured because Gerber Cereals are thoroughly pre-cooked to insure ready digestibility. This digestibility makes it possible to start cereal as soon as extra nourishment is indicated. Especially recommended as starting cereals: Rice Cereal and Barley—one grain and hypo-allergenic.

1. A.M.A. Journal of Diseases of Children, 95: 109-119, 1958.

2. Publication 589, National Academy of Sciences—National Research Council, Washington, D.C.—1958.



Gerber MODILAC

Formula Preparation

The Modilac Standard Formula is based on 2½ fluid ounces (50 calories) of the 1:1 normal dilution per pound of body weight per day. Iso-caloric with breast milk, it provides ample fluid and good nutrition for the rapidly growing infant. A newborn formula for the first week providing 13 calories per fluid ounce may be prepared by diluting Modilac with 2 parts of water. It should be fed according to the infant's caloric requirements.

MODILAC ANALYSIS

	GM./fl. oz. Normal Dilution	Caloric Distribution
Protein	0.65	13%
Fat*	0.83	37%
Carbohydrate	2.47	50%

*53% Linoleic acid.

Vitamins and Minerals

Per Quart of Normal Dilution (1:1) for Infants

Vitamin A	3000 U.S.P. Units	Thiamine	0.55 mg.
Vitamin D	600 U.S.P. Units	Riboflavin	1.00 mg.
Vitamin C	45.00 mg.	Calcium	800.00 mg.
Vitamin B ₆	0.70 mg.	Phosphorus	605.00 mg.



VITAMIN ANALYSIS

	For Infants	For Young Children
Thiamine	320%	160%
Riboflavin	100%	67%
Niacin	4 mg.*	80%

*Minimum daily requirement for this nutrient has not been established for the ages indicated.

Rice Cereal
Barley Cereal
High Protein Cereal
Oatmeal
Mixed Cereal
Cereal Quads
(Assortment of
4 one oz. pkgs.)



Gerber CEREALS

One ounce supplies the proportions of the minimum daily requirements of nutrients as indicated at left.

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Babies are our business...our only business!®



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Control weight gain from test to term

Rx the anorexic with no reported contraindications

TENUATE suppresses appetite with no effect on heart rate, blood pressure, pulse or respiration,¹ no alteration of BMR.²

In a recent study of 105 patients who used diethylpropion (TENUATE) throughout their pregnancies,³ the following effects on weight were recorded:

Actual loss of weight.....	7 patients
No gain in weight.....	11 patients
Gain of less than	
3 pounds per month.....	55 patients
Gain of more than	
3 pounds per month.....	32 patients

DOSAGE: One 25 mg. tablet one hour before meals. To control nighttime hunger, an additional tablet may be taken in mid-evening.

SUPPLY: Bottles of 100 and 1000 light blue tablets.

REFERENCES: 1. Alfaro, R. D.; Gracian, V., and Schlueter, E.: *J. Lancet*, *In press*. 2. Huele, G.: *Michigan Acad. Gen. Pract. Symposium*, Detroit, 1959. 3. Nilsen, R. O.: *Cur. Therap. Res.* 2:102, 1960. 4. Horwitz, S.: Personal communication, 1959. 5. Spielman, A. D.: *Michigan Acad. Gen. Pract. Symposium*, Detroit, 1959. 6. Ravetz, E.: *Michigan Acad. Gen. Pract. Symposium*, 1959. 7. Decina, L. J.: *Exper. Med. & Surg.*, *In press*. 8. Scanlan, J. S.: Personal communication, 1959. 9. Kroetz and Storck: Personal communication, 1959.

TENUATE

(diethylpropion)

hunger control with less than
1% CNS stimulation^{2,4,9}



THE WM. S. MERRELL COMPANY
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TRADEMARK: TENUATE®

In over five years



...for the tense and nervous patient

Despite the introduction in recent years of "new and different" tranquilizers, Miltown continues, quietly and steadfastly, to gain in acceptance. Meprobamate (Miltown) is prescribed by the medical profession more than any other tranquilizer in the world.

The reasons are not hard to find. Miltown is a **known** drug. Its few side effects have been fully reported. ***There are no surprises in store for either the patient or the physician.***

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of clinical use...

Proven

in more than 750 published clinical studies

Effective

for relief of anxiety and tension

Outstandingly Safe

- 1 simple dosage schedule produces rapid, reliable tranquilization without unpredictable excitation
- 2 no cumulative effects, thus no need for difficult dosage readjustments
- 3 does not produce ataxia, change in appetite or libido
- 4 does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
- 5 does not impair mental efficiency or normal behavior

Miltown®

meprobamate (Wallace)

Usual dosage: One or two 400 mg. tablets t.i.d.

Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets;
or as MEPROTABS®—400 mg. unmarked, coated tablets.



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on the pathogenesis of pyelonephritis

"An inflammatory reaction here [renal papillae] may produce sudden rapid impairment of renal function. One duct of Bellini probably drains more than 5000 nephrons. It is easy to see why a small abscess or edema in this area may occlude a portion of the papilla or the collecting ducts and may produce a functional impairment far in excess of that encountered in much larger lesions in the cortex."¹

Recent experimental evidence in animals strongly supports the view that obstruction of the tubules in the medulla, as opposed to the cortex, predisposes the kidney to pyelonephritis,² and "... as few as 10 organisms injected into the medulla were capable of causing infection."³

The "exquisite sensitivity"⁴ of the medulla to infection highlights the importance of obstruction to the urine flow in the pathogenesis of pyelonephritis. "There is good cause to support the belief that many, perhaps most, cases of human pyelonephritis are the result of infection which reaches the kidney from the lower urinary tract."⁵

An agent, such as FURADANTIN, which has a specific affinity for the urinary tract and which is actively excreted by the cells of the tubules, as well as of the glomeruli,⁶ is particularly suited to meet the problems posed by the pathogenesis of pyelonephritis and the primary pathways of infection.

*in pyelonephritis
to eradicate the pathogens
no matter the pathway*

FURADANTIN

brand of nitrofurantoin

*high urinary concentration
glomerular filtration
tubular excretion*

effective at glomerular and tubular levels: In addition to simple glomerular filtration, FURADANTIN is actively excreted by the tubule cells.

rapid antibacterial action: Antibacterial concentrations of FURADANTIN are in the urine in 30 minutes.

broad bactericidal spectrum: FURADANTIN is bactericidal against a wide range of gram-positive and gram-negative bacteria including certain organisms resistant to other agents.

free from resistance problems: Development of bacterial resistance to FURADANTIN has not been a problem in over 8 years of extensive clinical use.

well tolerated—even after prolonged use: FURADANTIN is nontoxic to kidneys, liver and blood-forming organs. No monilial superinfection, staphylococcal enteritis, proctitis or anovular pruritus has ever been reported.

no cross resistance or cross sensitization with other drugs: FURADANTIN, a synthetic nitrofuran, is unrelated chemically to any other class of antimicrobial drugs; cross resistance or cross sensitization does not occur.

AVERAGE FURADANTIN ADULT DOSAGE: 100 mg. tablet q.i.d. with meals and with food or milk on retiring. **SUPPLIED:** Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

REFERENCES: 1. Schreiner, G. E., A.M.A. Arch. Int. M. 102:32, 1958. 2. Rocha, H., et al.: Yale J. Biol. & Med. 32:120, 1959. 3. Freedman, L. R.: Yale J. Biol. & Med. 32:272, 1960. 4. Freedman, L. R., and Beeson, P. B.: Yale J. Biol. & Med. 30:406, 1958. 5. Rocha, H., et al.: Yale J. Biol. & Med. 30:341, 1958. 6. Paul, M. F., et al.: Am. J. Physiol. 197:580, 1959.



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while they are planning
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they need your help
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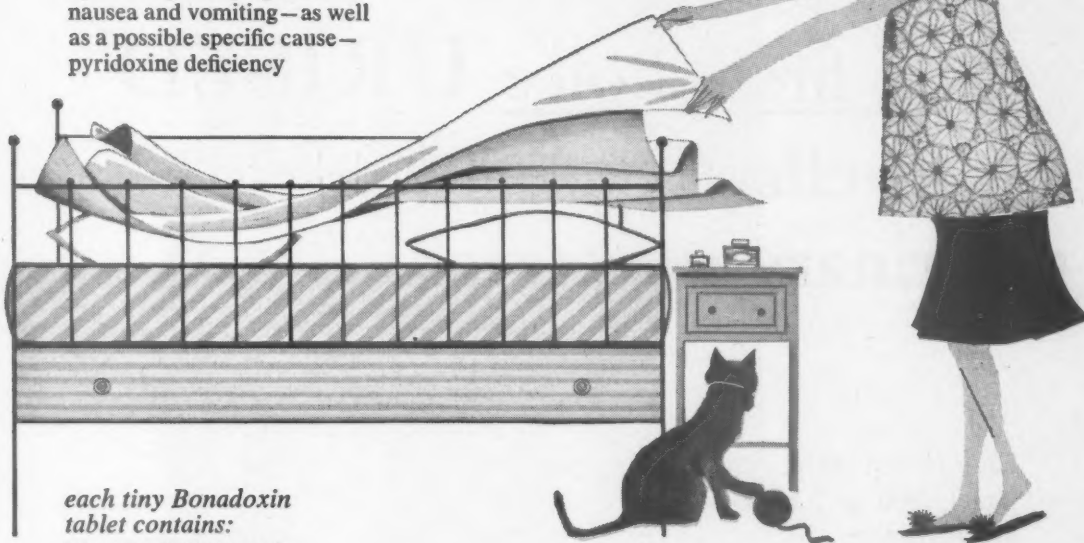
taken at bedtime

BONADOXIN®

STOPS MORNING SICKNESS IN 94%

**OFTEN WITH JUST
ONE TABLET DAILY**

by treating the symptom—
nausea and vomiting—as well
as a possible specific cause—
pyridoxine deficiency



*each tiny Bonadoxin
tablet contains:*

Meclizine HCl (25 mg.)
for antinauseant action
Pyridoxine HCl (50 mg.)
for metabolic replacement.

usual dose: One tablet
at bedtime; severe cases may
require another tablet on arising.

supply: Bottles of 25 and 100 tablets.
Bonadoxin also effectively relieves
nausea and vomiting associated with:
anesthesia, radiation sickness,
Meniere's syndrome, labyrinthitis,
and motion sickness. Also useful in
postoperative nausea and vomiting.

Bibliography on request.

For infant colic, try
Bonadoxin Drops. Each cc.
contains: Meclizine 8.33 mg./
Pyridoxine 16.67 mg.



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Urised combats bacteria while providing soothing relief in cystitis, urethritis, pyelitis, pyelonephritis, and prostatitis. Urised avoids toxic reactions or drug resistance.

as a first choice **URISED[®]**
is effective in 80 to 90%
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Each Urised tablet contains: Atropine Sulfate 1/2000 gr., Hyoscyamine 1/2000 gr., Methenamine, Methylene Blue, Benzoic Acid, Salol and Gelsemium. *Supplied:* Bottles of 100.

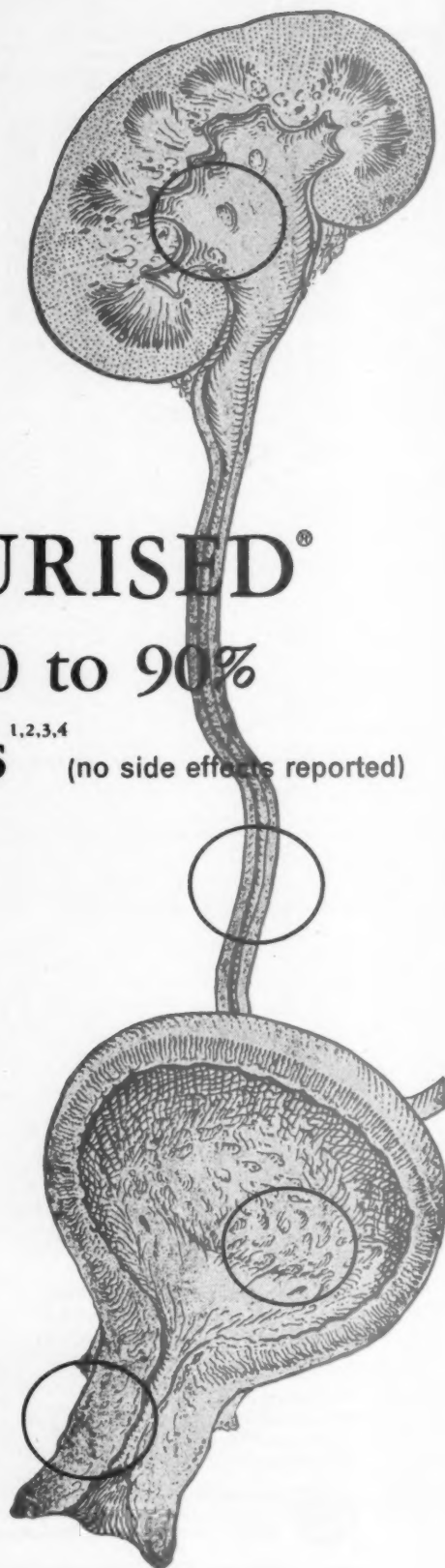
(1) Marshall, W.: Clin. Med. 7:499-502, 1960; (2) Haas, J., and Kay, L. L.: Management of Urinary Tract Infections (to be published); (3) Renner, J., et al.: Urinary Tract Infections: Treatment with Antiseptic-Antispasmodic Agent (to be published). (4) Strauss, B.: Clin. Med. 4: 309-310, 1957



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XYLOCAINE®

LOCAL ANESTHETIC



In the final analysis, only clinical experience can assure the survival of a drug. It is therefore gratifying to know that the performance of Xylocaine, in both dentistry and medicine, appraised in the light of current findings, confirms the original observations made more than a decade ago. Xylocaine has stood the test as a reliable and highly effective local anesthetic.

Surgery: infiltration nerve block and topical

Xylocaine is well suited for infiltration and nerve block techniques for a large number of major and minor operative procedures. Xylocaine gives anesthesia of adequate duration, is fast acting with high diffusibility, and its action is predictable. Minimal dosage consistently produces profound anesthesia. The margin of clinical safety is wide, and side effects, considering the extensive use of Xylocaine, are rare. For infiltration, 0.25% and 0.5% solutions are used in volumes of 30 cc. to 100 cc. The 1% solution may be used when smaller volumes of 10 cc. to 30 cc. are to be administered. When a single injection of Xylocaine is used for peridural, spinal and other



major nerve blocks, the concentration and volume varies with the type of block and the individual requirements. The total dosage of Xylocaine should *not* exceed 500 mg. when administered with epinephrine, or 300 mg. without epinephrine. Xylocaine is one of the very few local anesthetic agents which are effective topically as well as by injection. This is an important advantage in many surgical procedures where mucous membranes of the respiratory, upper gastrointestinal and lower genitourinary tracts, the eye and ear, and the anorectal area are involved. The 2% and 4% concentrations of Xylocaine solutions are used for topical anesthesia. Volumes are adjusted according to the requirements of the surgical procedures being undertaken.

Obstetrics, gynecology, urology: peridural & caudal, spinal "saddle block"

Spotty anesthesia, once a major drawback of peridural and caudal techniques, occurs only rarely with Xylocaine because of its high anesthetic index, wide diffusibility, short latency period, and adequate duration of nerve block. Its relative safety and reliability of performance has caused Xylocaine to be called a "... drug of choice for extradural analgesia."⁴ Because of the specific dosage requirements for extradural anesthesia, two strengths of Xylocaine, 0.8% and 1.2% are packaged in 30 cc. single dose containers. Operative analgesia is obtained with volumes of 25 cc. to 30 cc. of



0.8% Xylocaine HCl. Concentrations of up to 2% have been used for peridural anesthesia where complete muscular relaxation is required; this condition can, in many instances, be achieved with Xylocaine HCl 1.2%. "Xylocaine spinal" may be used with predictable results for obstetrical, gynecological and urological procedures, and for surgery of the lower abdomen and the lower extremities. "Xylocaine spinal" has a low binding affinity that minimizes potential nerve injury. Its anesthetic effect is routinely rapid, profound, well tolerated and free from "spottiness." It is completely stable in the presence of spinal fluid. The anesthetic action of "Xylocaine spinal" is of moderate duration, averaging 100 minutes, followed by another 40 minutes of analgesia.

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General use: injectable and topical anesthesia

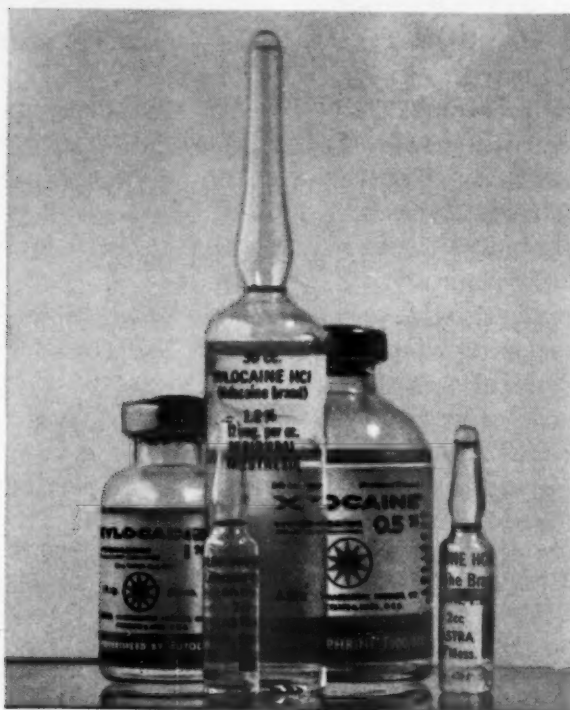
The general practitioner, the internist, and the surgeon alike are frequently called on to relieve pain or perform minor surgical procedures that may be successfully managed with the aid of this versatile anesthetic. Consistently effective anesthesia may be expected from Xylocaine because of its fast and profound action and spreading ability. It is virtually nonirritating to tissues and is relatively nonsensitizing, and possesses a wide margin of safety. For topical anesthesia Xylocaine may be applied as a spray, with cotton swabs, or by packs, as well as by instillation into a cavity and by application onto a surface. Local anesthesia of nerves, plexuses or terminal nerve endings requires indi-

Xylocaine®
(brand of lidocaine*)



vidualized volumes and concentrations. For general use Xylocaine is recommended in concentrations of 0.5%, 1% and 2%, with the 2% solution generally used for nerve block. Minimal volumes of 4% Xylocaine may be used topically in those cases where lower concentrations are ineffective or inadequate. The 4% solution may also be used transtracheally and for retrobulbar injection.

Indications for topical application: Lacerations, abrasions, burns, corneal analgesia, indirect laryngoscopy, pruritus. Indications for injectable anesthesia: suturing, wound closure, caesalgia, minor surgery, removal of moles, warts, and cysts, fracture reduction, bursitis, post-traumatic syndrome, herpes zoster.



For Infiltration and Nerve Block ■ Xylocaine HCl 0.5% and 1% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials. Xylocaine HCl 2% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials; also 2 cc. ampules (10's and 30's).

For Spinal Anesthesia ■ Xylocaine HCl 5% with glucose 7.5% (specific gravity 1.030-1.035) in 2 cc. ampules (10's and 100's).

For Peridural Anesthesia ■ Xylocaine HCl 0.8% and 1.2% without and with epinephrine 1:200,000 in 30 cc. single dose containers. For Continuous Peridural Anesthesia ■ Xylocaine HCl 1% without epinephrine in 100 cc. single dose containers.

For Transtracheal Use and For Retrobulbar Injection ■ Xylocaine HCl 4% without epinephrine in 5 cc. ampules (10's).

For Topical Application ■ Xylocaine HCl 0.5% and 1% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials. Xylocaine HCl 2% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials; also 2 cc. ampules (10's and 30's). Xylocaine HCl 4% without epinephrine in 50 cc. screw-cap bottles. (NOTE: This dispensing form is never to be used for injection.) Also available for topical use, Xylocaine Ointment 2.5% and 5%, Xylocaine Jelly 2%, and Xylocaine Viscous 2%.

Write for additional complete information concerning specific Xylocaine usage.

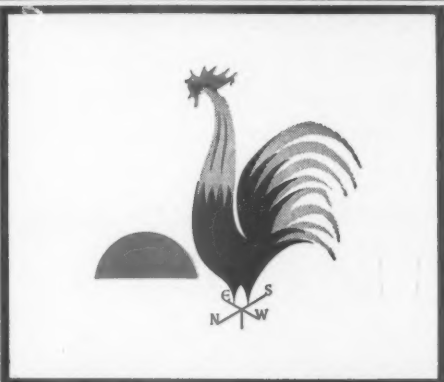
†Bryce-Smith, R.: Local analgesic drugs, Brit. M.J. 1:1039 (April 2) 1960.

by every
standard

the drug for
"morning sickness"

Bonine[®]

brand of meclizine hydrochloride



only rarely does
one drug meet
so well the needs
of one condition

IN BRIEF

BONINE is an antiemetic which provides rapid and prolonged protection against nausea and vomiting due to a variety of causes. A single dose of BONINE is usually effective for 24 hours. Thus, BONINE can be taken at bedtime to help prevent "next morning" sickness.

INDICATIONS: Valuable in the symptomatic relief of nausea and vomiting of pregnancy. Also indicated for motion sickness, radiation sickness, vertigo associated with Ménière's syndrome, labyrinthitis, fenestration procedures, vestibular dysfunction, and dizziness associated with cerebral arteriosclerosis.

ADMINISTRATION AND DOSAGE: For control of nausea and vomiting of pregnancy, a daily dose of 25 to 50 mg. is usually effective. For dosage schedules in other indications, see package insert.

SIDE EFFECTS: Not a phenothiazine, the side effects reported in association with BONINE have been mild and/or transient and consist of occasional drowsiness, dryness of the mouth, and blurred vision. Drowsiness is seen less frequently with BONINE in therapeutic dosages than with most other effective antiemetics.

PRECAUTIONS: As with other antihistaminic compounds, the physician should inform patients of the need for caution in driving a car or when engaged in other activities requiring alertness. There are no known contraindications to BONINE.

SUPPLIED: BONINE Tablets, scored, tasteless, 25 mg. BONINE Chewing Tablets, mint-flavored, 25 mg. BONINE Elixir, cherry-flavored, 12.5 mg. per teaspoonful (5 cc.).

More detailed professional information available on request.

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"We consider Doxidan to be superior to the agents we have previously employed in the treatment of constipation in postpartum patients. Not only was it more effective, but also its use was associated with almost complete freedom from side effects . . . flatulence, cramping and 'griping' were notably absent . . . 'rebound constipation' and the danger of subsequent habit formation are largely obviated by the use of this logical combination of a potent fecal softener with a mild peristaltic stimulant."¹

DOSAGE AND SUPPLY: One or two capsules administered at bedtime for two or three days or until bowel movements are normal. Each maroon Doxidan capsule contains 50 mg. Danthron (1,8-dihydroxyanthraquinone) and 60 mg. calcium bis-(dioctyl sulfosuccinate). Bottles of 30 and 100 soft gelatin capsules.

1. Bell, A.: Management of Constipation in the Puerperium. Accepted N. Y. S. J. Med.



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...with rapid disintegration time

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**gives them the benefits of:
two effective ingredients**

Oretic. Potent oral diuretic/antihypertensive producing maximum elimination of water, sodium, with minimum potassium loss.

Harmony. Fully as potent as reserpine in lowering blood pressure, Harmony has a lower incidence of such side effects as daytime lethargy, drowsiness, nasal stuffiness.

three precision dose forms

Oreticyl Forte. Oretic 25 mg.,
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Recommended "starter" therapy in most cases of established hypertension. Usual dose: one t.i.d.

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Harmony 0.125 mg.

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Either 25 or 50 strength recommended for adjustment of dose once response is seen. Dosage must be determined by patient's needs.

All 3 strengths, bottles of 100 and 1000.

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in progesterone deficiency states...

NORLUTIN[®]

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potent oral progestational agent

Oral therapy for "...a prompt and strong progestational effect on the human endometrium...."*

In gynecologic and obstetric disorders associated with progesterone deficiency, clinically desirable results can often be obtained with small oral doses of NORLUTIN. This orally administered agent is comparable in physiologic effect to parenterally administered progesterone. NORLUTIN thus provides effective therapy *by mouth*—a route of administration that secures patient cooperation and helps to assure an uninterrupted regimen.

Indications: Conditions involving deficiency of progesterone, such as amenorrhea

- menstrual irregularity • functional uterine bleeding • endocrine infertility
- habitual abortion • threatened abortion • premenstrual tension • dysmenorrhea

supplied: 5-mg. scored tablets, bottles of 30.

*Rock, J.; García, C.-R., & Pincus, G.: *Am. J. Obst. & Gynec.* 79:758, 1960.

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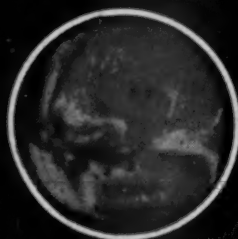


explodes trichomonads

VAGISEC®

LIQUID AND JELLY

**93.1% "cure" rate using
strictest criterion—
negative cultures for
3 consecutive months**



before VAGISEC



30 days "cure"

Repeated negative cultures, following treatment with VAGISEC liquid and jelly, confirmed "cures" in 93.1% of trichomoniasis patients (54 of 58) treated by Giorlando and Brandt.¹ These patients were followed up, using cultures, for a minimum of three months, many for as long as eight months. *All* remained negative. Using the same strict criterion of negative cultures, Weiner achieved comparable success²—46 of 51 patients freed of trichomonads.

VAGISEC therapy is consistently characterized by immediate relief of painful symptoms—few recurrences.

To help rule out conjugal re-infection—Husbands willingly cooperate as a part of the wife's treatment when RAMSES,[®] the pure gum rubber prophylactics with "built-in" sensitivity, are suggested for use routinely.

Active ingredients in VAGISEC liquid: Polyoxyethylene nonyl phenol, Sodium ethylene diamine tetra-acetate, Sodium dioctyl sulfosuccinate. In addition, VAGISEC jelly contains Alcohol 5% by weight.

1. Giorlando, S. W. and Brandt, M. L.: Am. J. Obst. & Gynec. 76:666 (Sept.) 1958. 2. Weiner, H. H.: Clin. Med. 5:25 (Jan.) 1958.

VAGISEC and RAMSES are registered trade-marks of Julius Schmid, Inc.

JULIUS SCHMID, INC.
423 West 55th Street, New York 19, N. Y.

women of childbearing age...
and growing children...

are
depleting their
iron
reserves

Iron deficiency anemias occur most often among women of childbearing age and growing children. Unless extra iron is provided, children's high growth requirements and women's iron loss from menstruation may dangerously deplete iron reserves. Many clinicians regularly prescribe a hematinic for six weeks each year during a woman's reproductive years. Children and adolescents are kept on intermittent iron therapy.

Livitamin, with peptonized iron and B complex, provides effective iron therapy with minimal side effects. Unlike many hematinics, Livitamin is pleasant tasting and well tolerated. Peptonized iron has as high a rate of absorption and storage, and is much less irritating than ferrous sulfate. B complex and other ingredients provide integrated nutritional support.

LIVITAMIN[®]

with Peptonized Iron

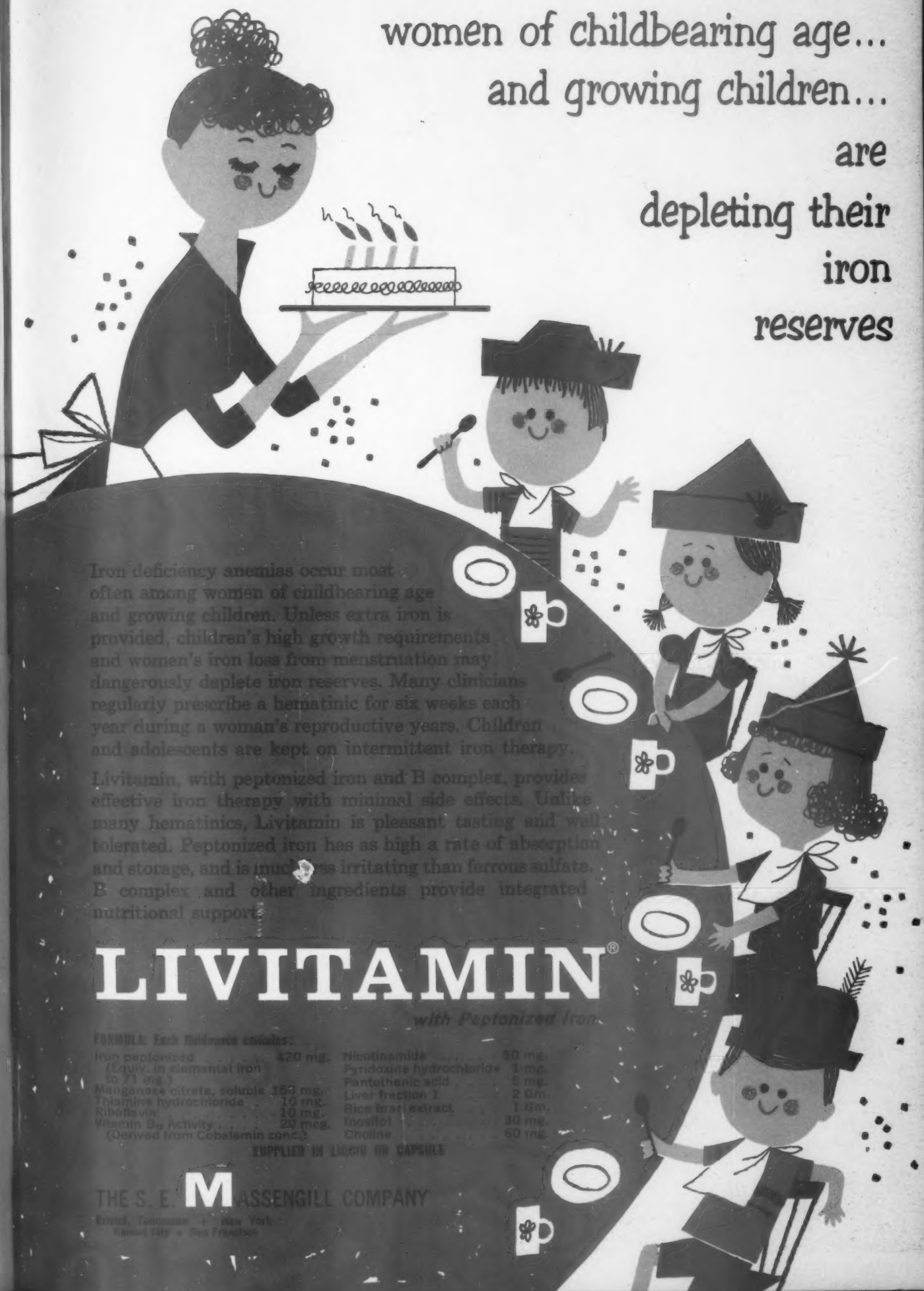
FORMULA: Each fluid ounce contains:

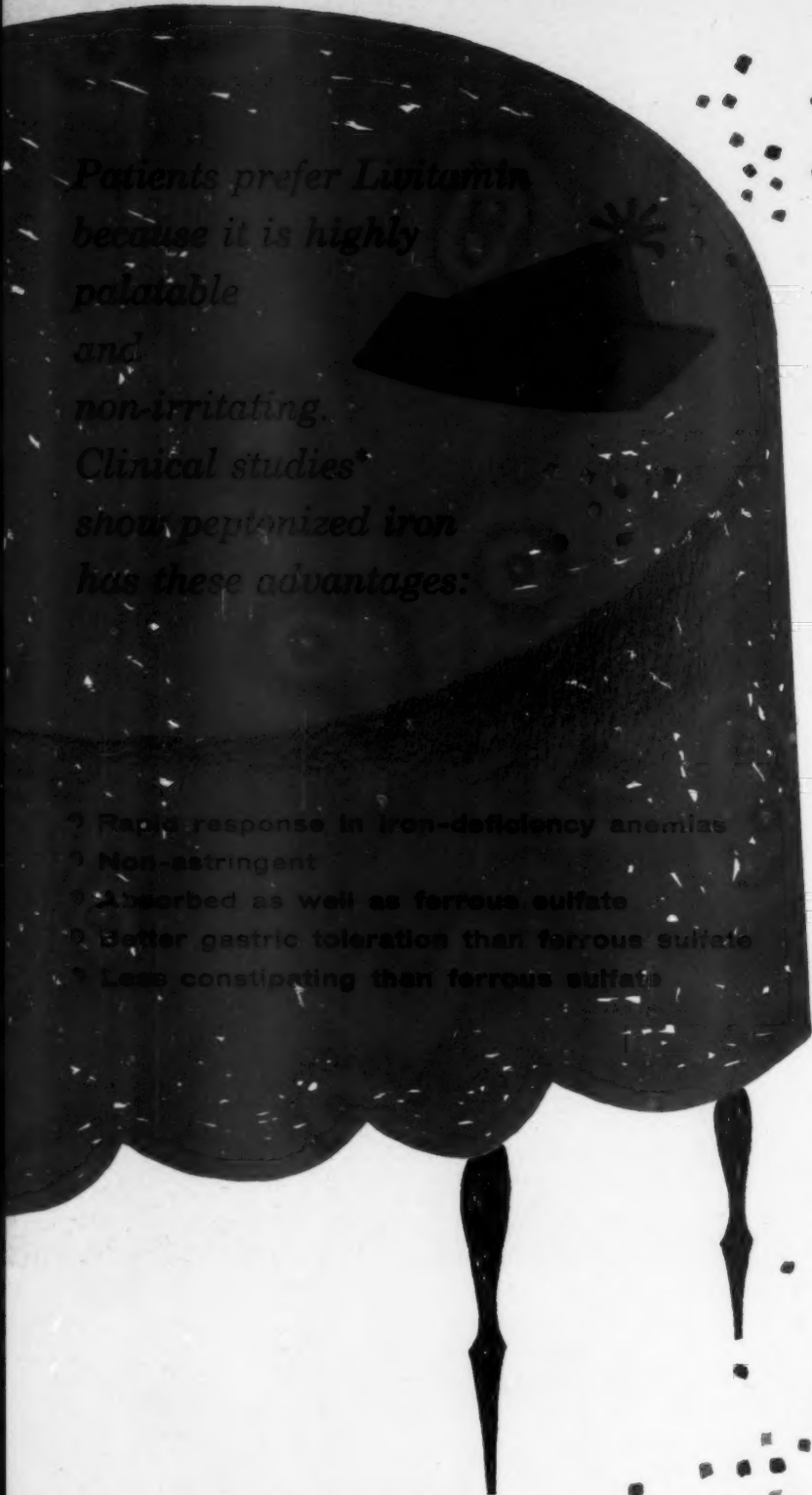
Iron peptonized	320 mg.	Nicotinamide	50 mg.
(Equiv. in elemental iron to 71 mg.)		Pyridoxine hydrochloride	1 mg.
Manganese citrate, soluble	150 mg.	Pantothenic acid	5 mg.
Thiamine hydrochloride	10 mg.	Liver fraction 1	2 gm.
Riboflavin	10 mg.	Rice bran extract	1 gm.
Vitamin B ₁₂ Activity	20 mcg.	Inositol	30 mg.
(Derived from Cobalamin conc.)		Choline	60 mg.

SUPPLIED IN LIQUID OR CAPSULE

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*Patients prefer Livitamin
because it is highly
palatable
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Clinical studies
show peptonized iron
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LIVITAMIN[®] *with Peptonized Iron*

... the preferred
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*Keith, J.H.: Utilization and Toxicity of Peptonized Iron and Ferrous Sulfate, Am. J. Clin. Nutrition 1:35 (Jan.-Feb., 1957).

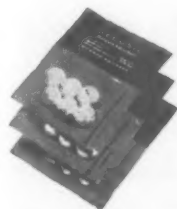
THE S. E. **M**ASSENGILL COMPANY Bristol, Tennessee • New York • Kansas City • San Francisco



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With pleasant-tasting Gelusil tablets you can start relieving her "heartburn" even before she leaves your office. And by giving her her initial medication, she can be maintained comfortably until she can get to her drug-

store for a full supply of Gelusil tablets or liquid. Gelusil neutralizes *and* adsorbs excess acid—protectively coats the mucosa with two long-lasting, demulcent gels—contains no irritating, constipating or laxative agents.



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the physician's antacid



in edema of pregnancy

"gratifying relief..."

in all patients

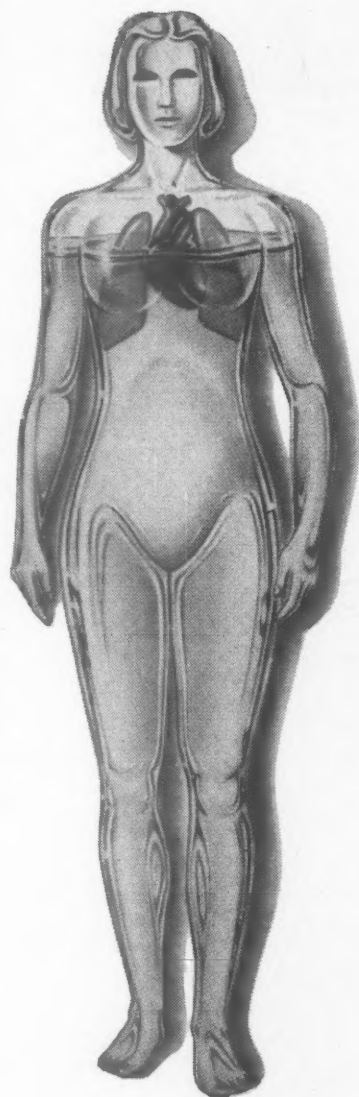
treated with



HYDRODIURIL[®]

HYDROCHLOROTHIAZIDE

increased potency—without corresponding increase in side effects



Ford, Ralph V.: Southern Med. J. 52: 40, (Jan.) 1959

“Hydrochlorothiazide was given to patients with edema (mild to moderate) of varied etiology...”

“There were...5 women in the third trimester of pregnancy.” In these patients the cumulative weight loss was 2 pounds after seven days of therapy and 4 pounds after twenty-one days. Gratifying relief of edema was observed in all patients.

DOSAGE: One or two 50 mg. tablets HYDRODIURIL once or twice a day, depending upon the condition and individual patient response.

SUPPLIED: 25 mg. and 50 mg. scored tablets HYDRODIURIL (Hydrochlorothiazide) in bottles of 100 and 1,000.

HYDRODIURIL is a trademark of Merck & Co., INC.


Additional information on HYDRODIURIL is available to the physician on request.

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when reassurance
is not enough...

Ritalin[®]
helps brighten the day

**Clinicians report how
RITALIN gives
dispirited patients
a lift...with safety**

"These patients represented the types of cases which might come into any doctor's office for treatment...the chronically ill and incurables, the convalescing group, the 'low' patients, depressed because of pressure of present-day living, and the group who were on medications which caused depressed states."

"The effect [of Ritalin] lasted about four hours, gave the patient a feeling of well-being and that life was worth living. Their worries seemed to disappear; they were alert, fatigue disappeared, and they could go all day without tiring. The effects gradually disappeared with no extreme let-down or rebound effect."

"... the drug [Ritalin] had no effect on blood pressure, the blood count, urine or blood sugar, did not depress the appetite, and produced no tachycardia. There was no evidence of any allergic manifestations in any of the cases."

—Natenshon, A. L.: *Dis. Nerv. System* 17:392 (Dec.) 1956.

"A double blind study of the mood elevating properties of Ritalin[®] in 112 patients showed statistically significant effect. . . . This drug offers great help in patients in whom elevation of the mood is desirable."

—Landman, M. E., Preisig, R., and Perlman, M.: *J. M. Soc. New Jersey* 55:55 (Feb.) 1958.

"It [Ritalin] causes mild depressions to vanish. . . . It changes dull, apathetic patients into more alert, interested ones."

"It stimulates apathetic and negativistic patients to more normal, productive activity."

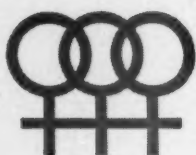
—Pennington, V. M.: *Mississippi Doctor* 35:57 (Aug.) 1957.

Complete information available on request.

SUPPLIED: TABLETS, 5 mg. (yellow), 10 mg. (light blue), 20 mg. (peach-colored)

RITALIN[®] hydrochloride
(methylphenidate
hydrochloride CIBA)

CIBA
SUMMIT, NEW JERSEY



Each tablet contains:

Provera (medroxyprogesterone acetate) 2.5 mg.
 Cardrase (ethoxzolamide) 35 mg.
 Levanil (ectylurea) 300 mg.

DOSAGE: 1 tablet 1 or 2 times daily, 5-10 days
 before the period.

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CYTRAN[®]

GETS AT THE CAUSE

to restore hormonal balance...

corrective therapy Because Cytran contains the new progestin, Provera,[†] you can now reach the *cause* of premenstrual tension—hormonal imbalance. Estrogen-progesterone ratio is adjusted to more normal premenstrual balance. Thus even abdominal discomfort, shakiness, fatigue—symptoms incompletely controlled by mere symptomatic treatments—are effectively relieved.

to comfort the patient...

symptomatic therapy An effective diuretic (Cardrase[†]) and a mild tranquilizer (Levanil[†]) afford symptomatic relief while Provera works to effect a restoration of hormonal balance. They also supplement the activity of Provera in those rare cases where restoration of hormone balance does not completely eliminate edema and anxiety/tension.



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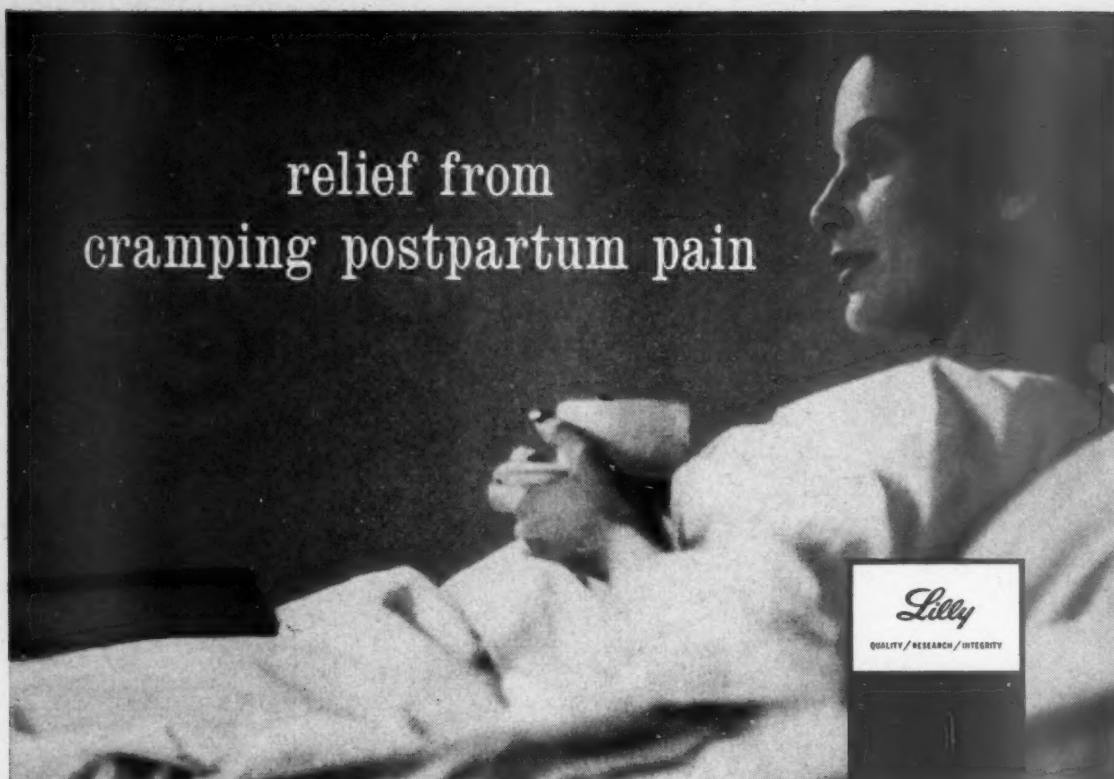
† TRADEMARK, REG. U.S. PAT. OFF.

Upjohn

OF PREMENSTRUAL TENSION



relief from
cramping postpartum pain



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Both forms combine the analgesic advantages of Darvon® with the anti-pyretic and anti-inflammatory benefits of A.S.A.® Compound. Darvon Compound-65 is indicated when *increased* analgesia is desired without increase in salicylate content or the size of the Pulvule®.

Formulas

DARVON COMPOUND		New DARVON COMPOUND-65	
32 mg.	Darvon	65 mg.	
162 mg.	Acetophenetidin	162 mg.	
227 mg.	A.S.A.®	227 mg.	
32.4 mg.	Caffeine	32.4 mg.	

Usual Dosage: *Darvon Compound*: 1 or 2 Pulvules three or four times daily.

Darvon Compound-65: 1 Pulvule three or four times daily.

Also Available: Darvon, in 32 and 65-mg. Pulvules • Darvo-Tran®

Darvon® Compound (dextro propoxyphene and acetylsalicylic acid compound, Lilly)
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American Journal of Obstetrics and Gynecology

Transactions of the Eighty-third
Annual Meeting of the
American Gynecological Society

Thomas Stephen Cullen

Presidential address

KARL H. MARTZLOFF, M.D.

Portland, Oregon

I GREATLY appreciate the honor this Society has bestowed upon me, and now, at the closing of my term of office, I wish to express my warmest thanks. My feelings run deeper than words can convey.

Since becoming a Fellow, I have felt the ensuing years richly rewarding, both by contact with and knowledge gained from this body of gentlemen of such recognized professional accomplishments. In fact, one cannot be a member of this Society and not have met outstanding personalities. It is of one of these that I would like to respectfully talk this morning. One whom it has been my privilege to know, one who encouraged and stimulated me in my early years—Dr. Thomas Stephen Cullen, a distinguished member of our Society, an important con-

tributor to our scientific literature, and a prominent citizen of his community.

Thomas Stephen Cullen was elected to membership in 1904 at the age of 36, became a life member in 1935, and died March 4, 1953, when 85 years of age. Although he was probably one of our most outstanding and best known members, it is interesting to note that during his 49 years of membership he held office only once, serving on the Council in 1914. These comments are designed to be neither fault-finding nor critical, but only to afford an interesting side light to a distinguished, though not a particularly popular, individual. It may seem strange that a man so generous, kind, and thoughtful, who always enjoyed the confidence and loyalty of his staff, should lack popular appeal. Always genuinely appreciative and punctilious in acknowledging a kindness or a favor, he nevertheless gave the impression of being constantly pressed for time

Presented at the Eighty-third Annual Meeting of the American Gynecological Society, Williamsburg, Virginia, May 30-June 1, 1960.

and of being self-sufficient to the point of apparent brusqueness. Examples of his personal generosity and detailed thoughtfulness are many. Probably as we unfold our story we may better understand this personality.

It is apparent that this biographical account is not of the conventional variety, since it is designed to omit minutiae and to highlight the vigorous facets of a fascinating career. A Canadian by birth and the son of a splendidly endowed, peripatetic Methodist minister, Tom Cullen's early years were spent in the rugged atmosphere of virgin timber, loggers, and sawmills of the late 1860's. Such was the start of our indefatigable gentleman endowed with as much or more misdirected energy than is generally attributed to ministers' sons. His love of the outdoors and the Canadian woods remained with him for life. His attachment to his family—father, mother, sisters, and his brother, Ernest—was a touching example of lifelong devotion and unselfish generosity.

At the age of 13 young Tom moved to Toronto, where his father had been assigned to a new parish. Now his original plan to study law gave way to a decision in favor of medicine, and he entered Toronto University Medical School in 1886, at the age of 17 years and 10 months. He also continued a newspaper route, begun 2 years before and faithfully carried on until he finished medical school, thus supporting himself and affording what aid he could to his family.

While at medical school he had as a classmate and friend Lewellys F. Barker, who was later to become one of the nation's outstanding internists and teachers. They were fellow interns at Toronto General Hospital and it was here in 1891 that Tom Cullen's medical career took its definitive direction. After observing Howard A. Kelly operate, while visiting in Toronto, young Cullen was so captivated by Kelly's precision and dexterity that he requested and obtained an internship on Kelly's staff at Johns Hopkins. On his arrival in Baltimore in the fall of 1891 a place on Kelly's service was not immediately available, but the kind hand of fate intervened and our young doctor,

through Kelly's efforts, was assigned to pathology for 3 months prior to entering the gynecological service. This temporary diversion into pathology proved both fateful and fortunate, for it marked the beginning of a lifelong friendship with William Welch, and it completely molded Cullen's future scientific interest into the field of pathological anatomy. This, of course, was a time of scientific ferment; only 65 years before the first achromatic microscope had been constructed in Paris (1824), and it was only 18 years since Waldeyer (1872) published his final paper demonstrating conclusively the epithelial origin of cancer. In fact, but 12 short years before (1878) Freund had performed the first abdominal operation for cancer of the uterus, Ruge and Veit had published their first monograph on cervical portio cancer, and Robert Koch published his book, *The Cause of Wound Infections*, while a year later Louis Pasteur demonstrated puerperal fever generally to be caused by a streptococcus.

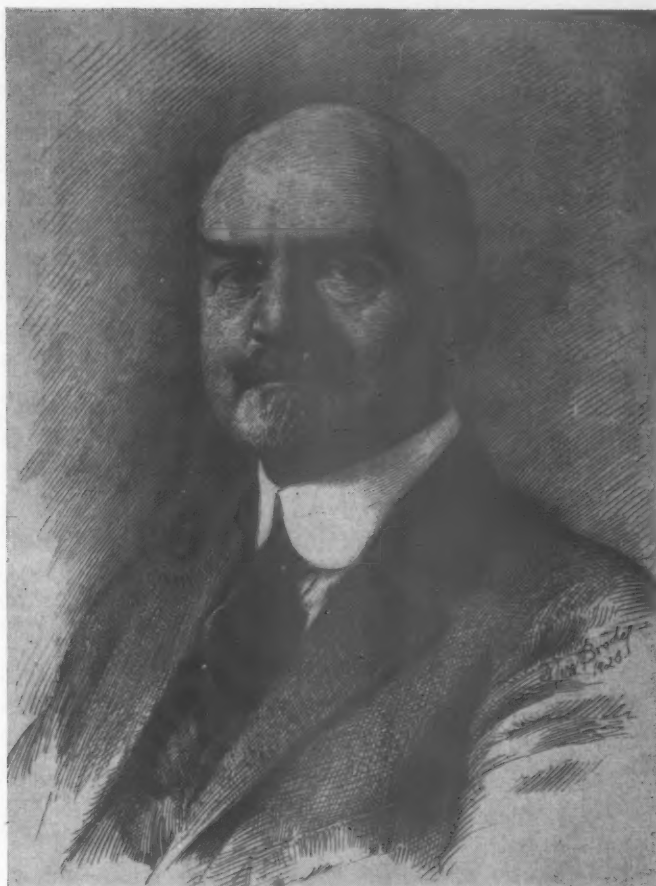
Truly, the microscope and test tube were beginning to show their influence. Many old ideas and misconceptions were going by the board as the tidal wave of scientific medicine again was shaking the barnacles from the hull of medical progress.

In the midst of this turbulence, Tom Cullen found himself a member of a picked crew directed by a galaxy of intrepid, bold, and competent scientific mariners, William Osler, William Henry Welch, Howard Atwood Kelly, and William Stuart Halsted, themselves devotees of Pasteur, Lister, Koch, von Recklinghausen (typhoid bacillus), Cohnheim, Ludwig, and others. Here there were friendliness, bursting scientific curiosity, argumentation, shop talk, companionship, driving concentration, long hours of work, and satisfying fatigue for senior and junior staff.

Now out of the laboratory and finally as an intern on Kelly's service, Cullen was abruptly precipitated into a Halstedian surgical innovation nonexistent elsewhere, namely, washable white cotton shirt, pants, and caps. This was the era before rubber gloves when

THOMAS
STEPHEN
CULLEN

(From etching by Max Brödel)



senior surgeons generally operated in frock coats with cuffs turned back. During the ensuing year he witnessed and assisted in a type of surgery no where else to be seen.

Having completed his first year's surgical service, penniless Cullen obtained a \$600 loan from Kelly and a 6 month leave of absence which permitted him to embark on a thrilling scholastic safari to Göttingen. Here he spent 6 months in the laboratory of the great Johannes Orth, a favorite pupil and disciple of the renowned Rudolf Virchow. He also visited Leipzig, Vienna, Paris, and London, meeting Zweifel, Menge, Koenig, Pozzi, and others. On returning to Baltimore, he found that his anticipated appointment to the residency in gynecology had fallen through. So, at the age of 24, flat broke and in debt, he returned again to Welch's laboratory (1893). Here for the next 3 years, under the stimulating influence of Welch and Kelly,

he had charge of gynecological pathology, discovered and began using the Surgeon General's library regularly, and published 14 papers. One of these concerned his technique for a rapid method of making permanent preparations from frozen sections by the use of formalin. This proved to be a basic contribution to the rapid frozen section technique now in common use.

Another important contribution at this time developed from his observations and studies on diffuse uterine adenomyosis. These led him to the conclusion that the glandular structures occurring in the myometrium were of endometrial derivation (1895), thereby differing with the famous German pathologist, von Recklinghausen, who considered these glandular inclusions to be of Wolffian body origin. It was thought by some that this difference of opinion resulted in a long period of ill will on the part of von Reck-

linghausen. This, however, was incorrect, for von Recklinghausen accepted Cullen's findings and interpretation, and they corresponded for years.

His activity in pathology resulted in an invitation to become professor of pathology at Vanderbilt. This was flattering but did not divert him from his long-cherished goal to return to Kelly's service, which he did in the fall of 1896. Now having attained this goal, Cullen, thoroughly impressed with the value of his own laboratory experience, felt that a prerequisite to the residency in gynecology should be a full year's training in gynecological pathology.* This suggestion was accepted by Kelly and became a departmental policy, and, through the collaboration of Welch, the first laboratory of gynecological pathology in America was established.

Our budding surgeon-pathologist, up to his ears in surgery with his chief, Kelly, was now gripping even more tightly the literary helm. At least two factors were involved in this stimulus; one the knowledge that his chief was preparing a two-volume book on operative gynecology and, finally, his own clinical observations of patients with far-advanced, neglected cancer. With encouragement from his chief, he began organizing material for a monograph on uterine cancer. To facilitate this Kelly promised financial backing to the extent of \$10,000 without security. The work on his first monograph started while he was still a resident and continued without interruption when he entered private practice in 1897, at which time he was appointed associate in gynecology and given charge of gynecological pathology. The fruit of this first major literary effort, *Cancer of the Uterus*, appeared in 1900. It was the first comprehensive monograph on uterine cancer. Beautifully and profusely illustrated, it comprised 693 pages, represent-

ing untold hours of labor and a cash outlay of \$6,000. True, other monographs had been published, such as that by Wagner, but none in any way comparable to this which almost overnight gave the author, now 32 years of age, an international reputation. The offer of a professorship in gynecology at Yale came just prior to its publication.

Interwoven with this first major effort were a number of history-making personalities without whose participation and encouragement the monograph would have fallen far short of its attained goal. The name of Kelly and his characteristically generous financial backing have been mentioned. Prominent and indispensable also was the work of the principal artist, Max Brödel, whose career was so intermingled with that of Cullen that it behooves me to digress at this point in order to give additional background.

This talented young artist came to Baltimore from Germany, at the suggestion of Franklin P. Mall, to work as an illustrator for Kelly. Mall had become acquainted with him in Ludwig's laboratory in Leipzig, in 1888, where young Brödel was working during vacations and had done some work for Mall, who evidently recognized his talent and potential value. On Mall's return to Baltimore from Chicago in 1893 to take charge of anatomy, he was so occupied with the organization of his department that he was unable to utilize the services of an artist.* Therefore, when Kelly recognized his need for a competent artist to illustrate his volumes on operative gynecology (to be published in 1898) Brödel was brought into his department in 1894, where he later became available to Cullen, with whom a lifelong friendship ensued.

It was soon apparent that this was a young man of many talents, who, though having been trained when a youth as a concert

*His conviction of the need of a thorough appreciation of pathology persisted to the point that in 1921, through the courtesy and cooperation of William G. MacCallum, the plan was amplified to include a year in general pathology as a prerequisite to gynecological pathology. This has been continued under the professorships of Arnold Rich and Ivan L. Bennett, Jr.

*However, by 1900, this need was felt and fulfilled by a skillful and charming young artist from Smith College, a Miss Ruth Huntington, who was later to become Mrs. Brödel.

pianist, was also a master of graphic art and its many techniques, an accomplished microscopist, gross anatomist, and investigator. There is little doubt that the attractiveness and value of Kelly's and Cullen's books, as well as the papers of many staff members, were enhanced by Brödel's artistry, adding both to the reputation of the authors and to the prestige of Brödel as a medical illustrator. During this interval, because of Kelly's recognition of his talent and financial support, Brödel started classes in medical illustrating for medical students who showed talent in this direction. So successful and popular were these classes that in 1905 (at the request of Kelly) Brödel was appointed instructor in art as applied to medicine. An inevitable outgrowth of this was the development of an unofficial school for medical art, still supported largely by Kelly, to which young professional illustrators were being attracted by this gifted artist.

Now that Cullen's first book was published it remained the single great unchallenged monograph* on uterine cancer until the voluminous and excellent German monograph by Schottlaender and Kermauner appeared 12 years later. Having made progress in private practice, Cullen experienced no comparable financial progress in the literary field, for his varied medical book ventures were to cost him between fifty and sixty thousand dollars. Also, he had decided to remain in Baltimore instead of accepting the invitation to Yale. Having been promoted to an associate professorship as a result of the Yale offer, he was still in charge of the laboratory and the teaching of gynecological pathology. He also operated on clinic patients one day a week and received an increase in remuneration of \$200 annually, making his total faculty pay \$400 a year. Always scrupulously careful to pay his debts, Cullen nevertheless showed an ap-

parent indifference to "hard cash." It is not surprising that financial consideration did nothing to deter our blossoming surgeon-author from becoming married in 1901 to Miss Emma Jones Beckwith* of Louisville, Kentucky.

Following his earlier critical study of myometrial endometriosis under the term "adenomyoma uteri diffusum," which had brought him into immediate scientific proximity to von Recklinghausen, Cullen pursued this study and in 1908 published his second book, a 270 page monograph on *Adenomyoma of the Uterus*. The literary "floodgates"† having been breached once more, they were to be opened wide the following year by a 723 page book titled *Myomata of the Uterus*. This was jointly authored with Kelly out of Cullen's gratitude to his chief, who never saw the text until it was published. From here on, although he published many case reports and papers on a variety of subjects, his underlying interest in endometriosis and its distribution continued. Lesions of the umbilicus which contained uterine mucosa accordingly provided the basis for a number of papers, which evidently so stimulated his interest in this structure that in 1916 he published his fourth monograph, a book of 680 pages on the *Embryology, Anatomy and Diseases of the Umbilicus*.

As we noted earlier, the artistry of Max Brödel was a priceless adjunct to the books written by Kelly and by Cullen; Brödel was, in fact, an indispensable collaborator. While it was his judgment that frequently decided the type and form of illustration to be used in a given situation, of equal importance were some of his dissections and microscopic studies. Many of these were original contributions so beautifully and accurately done that without them the publications they illustrated would have been practically meaningless. Particularly true was this of Cullen's

*Here Cullen gives the first clear description of intra-epithelial carcinoid alteration (cancer-in-situ) that I have seen in the English language. This occurred in the vicinity of a carcinoma and was regarded by him as a preinvasive stage of cancer.

*Mrs. Cullen died in September, 1918. Dr. Cullen married Miss Mary Bartlett Dixon, April, 1920.

†"Floodgates" is hardly an exaggeration because in 1910 Kelly published a 502 page revision of his monograph on *Appendicitis*.

books, which were designed as definitive reference monographs and not as textbooks. Brödel's complete indispensability, however, is brought out clearly in Kelly and Burnam's *Diseases of the Kidneys* and particularly strikingly in Cullen's last book and his two last major papers, "Accessory Lobes of the Liver," 46 pages, published in 1925, and "Lesions of the Rectus Abdominus Muscles," published in 1937 by Cullen and Brödel. Here Brödel's basic anatomical studies, descriptions, and drawings provided the major contributions.

For all practical purposes, Cullen's book publishing ended in 1916, when he was 48 years of age. His last published paper appeared in 1945, eight years before his death. Appropriately, it concerned his dear friend: "Max Brödel: Director of the First Department of Art as Applied to Medicine in the World." The title of this paper reflected one of Cullen's important nonscientific contributions to medicine. This began initially with his solicitation of funds in the amount of \$5,000 a year for 3 years from an anonymous donor to support Brödel's work, for a critical time had arrived for Brödel and the Medical School. Brödel's work for Kelly's books was to terminate in 1911 and the Mayo Clinic, aware of this, was seeking his services. Understandably, this represented a crisis of the first magnitude, not only from the standpoint of a deep personal loss for Cullen, but also as an irreparable disaster to a medical school that had no funds with which to support a department of medical art. For a period of 10 years, Cullen canvassed the nation seeking some generous individual who might be interested in endowing a chair of art as applied to medicine. The anonymous donor's original offer was renewed but with no assurance that this would or could be continued indefinitely. Despite these uncertainties the offers when made were promptly accepted by the University's Board of Trustees, thereby giving recognition to and assurance of the start of a new medical school venture which, however, could evanesce at any time unless an adequate endowment became available. For the University this meant

the possibility and responsibility of starting and then abandoning a department once well underway. For Cullen it presented the perturbing possibility of defeat in having started a lost cause. Consequently, every avenue was used by Cullen for approaching such men as J. P. Morgan, Henry Walters, John D. Rockefeller, Henry Ford, Mr. Eastman, Alfred DuPont, and others. A long-sought victory was brought about in December, 1921, when Henry Walters, the original annual donor of \$5,000, gave the University \$110,000 as a permanent endowment. Mr. Walters' identity as the Department's benefactor remained unrevealed until his death in 1931 when his name,* with Mrs. Walters' consent, was made known.

Cullen's cup of happiness was now full to overflowing: he was the author of 4 exhaustive monographs, a possessor of international reputation, and he finally had succeeded in obtaining for the University a permanent endowment to establish the first department of art as applied to medicine.

Many of the foregoing events were occurring against the subtle background of a massive curricular ground swell which was later to engulf the medical school clinical faculties in the problem of full-time clinical teaching. The vortex of this concept appeared to be initiated in Baltimore. Actually, its inception occurred long before, probably in the laboratory of Carl Ludwig, the German physiologist. Here Welch and particularly Mall were exposed to the theories, practices, and philosophies of German medical education. They became thoroughly indoctrinated with the view that a medical school should be, in fact, a department of a university and that the clinical faculties of a medical school should partake of the same scientific tenor as the laboratory divisions in order to raise clinical medicine to more acceptable academic levels. Here then was the seed of full-time clinical teaching, long dormant in Baltimore, but

*Cullen states that the department Mr. Walters endowed was given his name. There is, however, no evidence of record that the department was ever officially named for Mr. Walters.

now germinating in the person of Mall on his return from Clark University and the University of Chicago to assume the professorship of anatomy at Hopkins in 1893, almost 70 years ago.

By 1911, while Cullen was concerned so acutely with the possibility of Brödel's leaving Baltimore, the rising tide created by Mall's influence on Barker, Welch, and others favoring full-time clinical professorships reached its crest, in 1910, in the form of the so-called Flexner report. Bulletin No. 4 prepared by Abraham Flexner for the Carnegie Foundation for the Advancement of Teaching laid down a decimating barrage that effectively sank about half of America's moth-eaten medical school fleet and sprang leaks in many others.* A year later Mr. Flexner prepared for the General Education Board a "confidential report"† to determine how best a million dollars could be spent on Hopkins to help improve American Medical Education. The result of this was the introduction in 1913 of full-time professorships in medicine, surgery, and pediatrics endowed with one and a half million dollars by the Rockefeller Foundation.

It was at this time, while Cullen was seeking an endowment for Max Brödel and the School of Art, that he was simultaneously concerned and uncertain about his own future with the school. The full-time clinical teaching issue was now sharply drawn; chiefs, faculty, students, and extramural interests became enmeshed and chose sides. Long-standing friendships were strained and an unwholesome atmosphere of unrest permeated the institution when I first arrived. However, at no time did I hear any department head utter a word of criticism or even comment on the matter; thereby showing

wise restraint and decorum in dealing with subordinates. Nevertheless, the impact was a telling and continuing one, the extramural vibrations of which were ultimately widespread and truly disturbing to many who were not concerned primarily with clinical teaching.

This was a period when the Rockefeller Foundation dominance was so all-pervading that one gained the impression it controlled both school and hospital. Indeed, some laboratory scientists who came under this influence resented it, feared it, and viewed its ultimate outcome with apprehension. Unmistakably the preclinical laboratory disciplines had captured the clinical side and wanted to mold it into their ideological image. Therefore, for a time the emphasis on a clinician's qualifications was not based on his clinical training, knowledge, and talent, but on his laboratory background and presumed ability to do productive laboratory research. Overemphasis on laboratory skills for clinical teachers became so insistent that the Department of Medicine, particularly, experienced an influx of men, well-grounded in the laboratory disciplines, who were now supposed to become groomed in clinical medicine in order to assume directive clinical posts in other schools. During this interesting but confusing interval, I became impressed by the ineptness and the relative incapacity of these attractive, interesting, and intelligent men, who had spent most of their professional lives in the laboratory, to develop the acumen necessary for the proper and effective prosecution of clinical responsibilities.

How much Mall, Welch, and their group were influenced by the records of Halsted, Cullen, and Barker in their final point of view toward the qualifications of full-time clinical professors can hardly be surmised. Nevertheless, these were the prototypes with whom they were directly familiar. When Halsted came to Welch's laboratory, he was already regarded, according to Councilman, as the most brilliant of the younger surgeons of New York. He had shown an interest in investigation well known to Welch, having

*At this time there were 7 medical schools in Baltimore, 7 in Louisville, Kentucky, and 15 in Chicago.

†Despite Flexner's excellent and devastating Bulletin No. 4, it did not *ipso facto* qualify him, a layman, for this type of study, which revealed such bias, lack of perspective, and inaccuracy in its evaluation of the clinical activities at Hopkins that Osler, now Regius Professor of Medicine at Oxford, was constrained to write a letter of indignation to the President of the University repudiating Flexner's report for its "unfairness or ignorance."

demonstrated mandibular nerve block on himself by the use of cocaine, for which he unwittingly developed an addiction, being tragically unaware of its habit-forming character. While in Welch's* laboratory recovering from the frightening effects of his addiction, which he overcame, he again showed his investigative ability and with Mall† for the first time directed attention to the intestinal submucosa and its importance in intestinal suture (1887). It seems strange that the import of the intestinal submucosa should have been recognized so late since intestinal operations, both clinical and experimental, had been performed for years by many investigators, not the least of whom was the brilliant Bichat, who long before had recognized the ability of apposed serous surfaces to adhere. Here we also find Cullen (1891-1896) in an era where the last fundamental contribution to intestinal surgery had been made, while rubber gloves and surgical asepsis of a variety hitherto unknown were currently to be introduced by Halsted.

Cullen represented a reversal of Halsted's career, for he came to Welch's laboratory not as a skilled surgeon, but from an internship. Except for a short interlude on Kelly's service, he remained with Welch for 3 years. He was, therefore, recognized, initially, as a pathologist before returning to Kelly's service (1896) where the exactitudes of clinical surgery became indelibly etched by his experiencing in the operating room and on the wards the endless responsibilities and worries involved in caring for critically ill patients.

Additionally, there existed the far different example of Barker who had moved from Osler's service after one year in clinical medicine to Welch's laboratory (1892), where during the next 8 years he became associate professor of pathology. During this

interval he also became affiliated with the Department of Anatomy, being made associate professor by Mall. This was followed by his appointment to the professorship of anatomy at the University of Chicago where he remained for 5 years. Then back to Baltimore in 1905 where he accepted the professorship of medicine following Osler's departure for Oxford.

It is, therefore, understandable that the laboratory scientists, the prime movers in this saga of full-time clinical professorships, had a trifling attitude toward the exacting requirements of clinical medicine. They envisioned nothing naïve or unrealistic in their concept that an individual originally trained and steeped in the laboratory disciplines should find little difficulty in preparing himself and successfully undertaking a clinical teaching position. It was evidently felt, if in fact any consideration was ever given to this facet, that merely brushing against sick people on ward rounds and in the dispensary without first having undergone a rigorous, basic clinical training was adequate to convert a laboratory scientist into a thoroughly competent clinician. As far as I could observe, no such transformation ever occurred. As I viewed the problem, it is one thing to successfully transpose a laboratory scientist from one laboratory discipline to another *allied* one, as Mall and Barker so well illustrated. But it is quite another proposition to expect such a person to prove himself as a skilled clinician or as a competent worker in the laboratory of an unrelated science without initial rigorous basic preparation. Many laboratorians have yet to discover this.

At this time any investigative endeavor that revealed the remotest relation to a clinical problem was considered as scientifically undesirable. In fact, an applicant for a Rockefeller traveling scholarship at that time would be rejected summarily if the investigation he planned emitted the faintest clinical aroma. Obviously, ideological brainwashing is not new and not confined to any one idea, time, or place. However, the foregoing represented some of the considerations that gave Cullen cause for serious concern. The

*Welch knew Halsted when they were in New York; he was profoundly impressed then by his potentiality and invited him to his laboratory in 1886 and so befriended him that Halsted's devotion and gratitude to Welch never ceased.

†Mall was Welch's first Fellow in Pathology and a warm and lasting friendship developed between him and Halsted.

unrealistic stress being placed on pure laboratory preparation for full-time clinical teachers alarmed him and many of his clinical associates. While he recognized, on the basis of personal experience, the desirability of a good background in one of the pre-clinical laboratory sciences for a future clinician, he knew from experience that intensive training in clinical disciplines was also essential and an indispensable prerequisite.

It may be noted in passing that when Barker returned to Baltimore from Chicago to succeed Osler in 1905, he requested a full-time clinical professorship since he was one of the strong supporters of the inflexible full-time University system for clinical professors.* This the Trustees were then unable to grant. But now that the full-time chair was offered him and having had a direct experience with his clinical post and private practice he resigned from the Chair of Medicine,† because of "personal financial responsibilities."

From 1913 on Cullen's extraclinical activities became directed toward public affairs although, as was noted earlier, his last book, a monograph on the umbilicus, was published in 1916. Now, however, long convinced that some of the tragic results of cancer derived from lack of information available to the public he felt that something should be done to remedy this. This was accomplished (by Cullen and some of his confreres) through the offices of Samuel Hopkins Adams, a journalist already well known to the public for his exposé of patent medicine racketeering. Adams, after conferring with Cullen, Welch, and a few others, became so imbued with the importance of

giving the public more information about cancer that he published several magazine articles on the subject. The first of these, containing an endorsement signed by Cullen, appeared in the *Ladies' Home Journal* for May, 1913. A storm of criticism from many professional sources concerning his "unethical conduct" left him undaunted, for from here on the publicity campaign concerning cancer was in full swing as he had anticipated.

With the retirement of Kelly in 1919, as the first head of the Department of Gynecology, Cullen was appointed professor of clinical gynecology. A determined effort was now afoot to unite obstetrics and gynecology, for Williams had become full-time professor of obstetrics and he desired the unification, a position he had made clear during several preceding years.* The argument of "combined" versus "separate" departments was now in full play, since it was known in 1917 that Kelly's retirement† was imminent.

With the construction of the new Woman's Clinic building in 1923, the issue finally required definitive decision. After thorough reconsideration the Hopkins Medical Board decided, with the acquiescence of Williams, that the two departments should continue as separate units. This is the arrangement that continued for the next 37 years under Cullen and TeLinde.

Although the issues were clearly defined in principle, there was delay in putting them into practice and it was not until Jan. 24, 1927, that the gynecological operating suite in the new Woman's Clinic was finally ready for use. During the intervening 3 years Cullen and his senior staff were involved in

*In 1902, while at the University of Chicago, Barker gave an address "Medicine and the Universities" to the Western Alumni of The Johns Hopkins University. However, by 1911 he had receded from his earlier fixed point of view and now could see that alterations in the application of the system might be advantageously utilized.

†This post was accepted by Theodore C. Janeway in 1914. In 1917, he decided to resign his post and return to New York, for he felt that the full-time University System for Clinical Professors at Hopkins was too inflexible to be satisfactory. However, this decision remained unfulfilled due to his tragic, precipitate death from pneumococcus pneumonia at the age of 45.

*Williams' views were published in 1914, two years after Mr. Flexner's confidential report to the General Education Board. However, the views expressed by Flexner on Obstetrics and Gynecology were similar to those of Williams and obviously were obtained from him, for he did not confer with Kelly or Cullen.

†Kelly took indefinite leave of absence in 1917 and retired in 1919, at age 60, ten years prior to compulsory retirement time in order not to obstruct the full-time plan which he disfavored. At this time also it was decided by the Medical Board of the Hospital and the Advisory Board of the Medical Faculty that Gynecology was to be considered a special branch of General Surgery.

what Cullen has termed "hospital politics," a distracting, disturbing interlude, disruptive to peaceful meditation and effective, pleasant work. As a result, there was discussion concerning the advisability of making provision for the gynecological operating suite in the plans of the new surgery building, for Halsted had previously expressed his willingness and approval to have gynecology affiliated with surgery as a surgical specialty. However, a \$150,000 grant from the General Education Board of the Rockefeller Foundation provided for the addition of an extra floor to the new Woman's Clinic building to house the gynecological surgical suite. This was done to give Cullen's department complete and individual identity. It also revealed a reversal of attitude by the General Education Board, for in 1912 Flexner had given his opinion to the Board that the Department of Gynecology at Hopkins, if not abolished,* should be merged with the Department of Obstetrics. Flexner was a general educator, without medical background, and he had obtained the medical information on which he based his opinion from just a few Baltimore sources. Over the years, however, his original point of view gave way to a more fully developed background of information, illustrating that, although time itself does not change past events, it may and often does alter one's sense of evaluation.

Cullen was keenly conscious of the unwholesomely diversive and attritive effects of interdepartmental jockeying and bickering. His admonition was to "saw wood" and to avoid, if possible, these debilitating involvements, never uttering a critical word about any opponent. However, the intramural scraping together with the long uncertainty concerning the future of his department as well as his own future in the school were devitalizing elements that blunted an interest which previously had been all-consuming.

Since he was a dynamic individual, it naturally followed that his interests would be

directed increasingly into extramural activities. He now became a trustee of the American Medical Association and, in 1930, the recipient of an LL.D. from his old school, the University of Toronto, on the occasion of celebrating the opening of the Banting Institute. Cullen said that while he derived real happiness from this honor, only somewhat less was his satisfaction at seeing, in a front faculty seat, an ancient oppressor, his first physiology teacher by whom he had been "flunked." In 1932 his Hopkins academic title was changed from Professor of Clinical Gynecology to Professor of Gynecology.

Becoming involved in municipal, state, and interstate politics, where matters of health were concerned, was a natural outlet for a minister's son possessed of his sense of fairness and administrative ability. Consequently, he played an important role in having the Baltimore Department of Public Health taken out of partisan politics, and he was directly instrumental in having laws formulated that removed the state public health service from similar political influence. In 1929 he was appointed to the Maryland Board of Health, succeeding William Welch, who had retired.

His final great achievement in behalf of public health culminated in his successful efforts to have Chesapeake Bay freed of sewage contamination. This effort was implemented through the creation of a Chesapeake Bay Authority that used Federal funds, ignored state lines, and had Cullen as its chairman. A great sea food industry was thereby saved.

Because he was always a great user of the Surgeon General's Library, and therefore possessed of a keen appreciation of the value of adequate library facilities, it was but natural that Cullen should be interested in the Enoch Pratt Free Library, which is Baltimore's public library system. He became president of its board in 1938, at the age of 70, and continued in this capacity until his death.

At the age of 85, having experienced an earlier cerebral vascular accident, this great

*Quotation from letter of Osler to Ira Remsen "this is the department which the Angel of Bethesda in the fullness of his ignorance suggests should be, if not wiped out, at any rate merged with that of Obstetrics."

man, following attendance at a surgical meeting, returned home, retired, and had another stroke, which proved fatal. A peaceful, placid ending to a splendid, strenuous

career. Truly

He had fought a good fight,
He had finished his course,
He had kept the faith.

REFERENCES

- Barker, Lewellys F.: *Am. Med.* 4: 143, 1902.
Barker, Lewellys F.: *J. A. M. A.* 57: 613, 1911.
Barker, Lewellys F.: *Time and the Physician*, New York, 1942, G. P. Putnam's Sons.
Chesney, Alan M.: *The Johns Hopkins Hospital and The Johns Hopkins University School of Medicine. A Chronicle*, Baltimore, 1943 and 1958, The Johns Hopkins Press, vols. 1 and 2.
Chesney, Alan M.: Personal communication.
Cullen, Thomas S.: *Bull. M. Library A.* 33: 5, 1945.
Davis, A. W.: *Dr. Kelly of Hopkins*, Baltimore, 1959, The Johns Hopkins Press.
Flexner, A.: *Medical Education in the United States and Canada*, Bulletin No. 4, The Carnegie Foundation for the Advancement of Teaching, 1910.
Flexner, A.: *From the Report on The Johns Hopkins Medical School* (confidential).
Flexner, A.: *Medical Education*, New York, 1925, The Macmillan Company.
Flexner, A.: *I Remember—The Autobiography of Abraham Flexner*, New York, 1940, Simon & Schuster, Inc.
Flexner, S., and Flexner, J. T.: *William Henry Welch and the Heroic Age of American Medicine*, New York, 1941, Viking Press, Inc.
Janeway, Charles A.: Personal communication, 1960.
Janeway, Theodore C.: *Ed. Review* 55: 207, 1918.
MacCallum, W. G.: *William Stewart Halsted—Surgeon*, Baltimore, 1930, The Johns Hopkins Press.
Richardson, Edward H.: *A Doctor Remembers*, New York, 1959, Vantage Press.
Richardson, Edward H.: Personal communication, 1960.
Richardson, Edward H.: *Autobiography and Memoirs*, chaps. 12 and 13 (confidential, unpublished).
Robinson, Judith: *Tom Cullen of Baltimore*, London and New York, 1949, Oxford University Press.
Sabin, Florence R.: *Franklin Paine Mall—The Story of a Mind*, Baltimore, 1934, The Johns Hopkins Press.
TeLinde, R. W.: *Am. J. Obst. & Gynec.* 68: 1203, 1954.
Williams, J. Whitridge: *Am. J. Obst.* 70: 247, 1914.

Ovarian function following pelvic operation

An experimental study on monkeys

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THE uterus for many years, in numbers probably by now astronomical, has been removed in toto or in part. On some occasions the ovaries are also removed; at other times they are allowed to remain. One would think that by 1960 the effect of the removal of the uterus on the ovary and its function would be clear and not a subject of controversy; yet, this is not the case. American gynecologists may differ somewhat on their criteria for removing ovaries but they are, on the whole, conservative of these organs. Nevertheless, Grogan and Duncan¹ are of the opinion that the interests of the patient are best served by bilateral oophorectomy at the time of routine abdominal hysterectomy.

Grammatikati² in 1889 first undertook to determine experimentally the effect of hysterectomy on the ovary. He removed the entire uterus of rabbits and on subsequent histology examination found no ovarian change. Since that time—in addition to rabbits—dogs, rats, mice, opossums, guinea pigs, and even ferrets have been subjected to similar studies with findings often as divergent in number and degree as there have been investigators. A great many investigators have found no change in the residual ovary. On the other hand, a variety of alterations have been noted. Reynolds³ has

best summarized and collected reports of the various ovarian changes attributed to hysterectomy. In the rat, there may be a marked increase of interstitial cells, follicular atresia, and development of follicular cysts and prolongation of the life of corpora lutea. Prolongation of the life of the corpus luteum has also been observed in the guinea pig. In the rabbit, one of the favorite experimental animals, follicular atresia and degeneration and interstitial cell change with development of an interstitial body have been reported. These changes are said to be similar to those of ovarian senescence. Tenny⁴ has also noted these changes after tubal ligation in rabbits. He also found that the adrenal glands increased in size with thickening of the zona fasciculata and the appearance of large, clear cells in the zona reticularis.

In general, then, following hysterectomy in experimental animals, the basic functional changes reported are lengthening or irregularity of estrus cycles, inhibition of estrus with histology findings of follicular atresia, prolongation of the life of corpora lutea, and interstitial cell hyperplasia. The cause of these varied changes has been attributed to an endometrial or uterine hormone interference with ovarian innervation, or interference with ovarian blood supply.

It is important to note that all the above changes were found in the rabbit, rat, and guinea pig. These are good general experimental animals but are not good animals to use in the study of human problems of reproductive physiology since these animals

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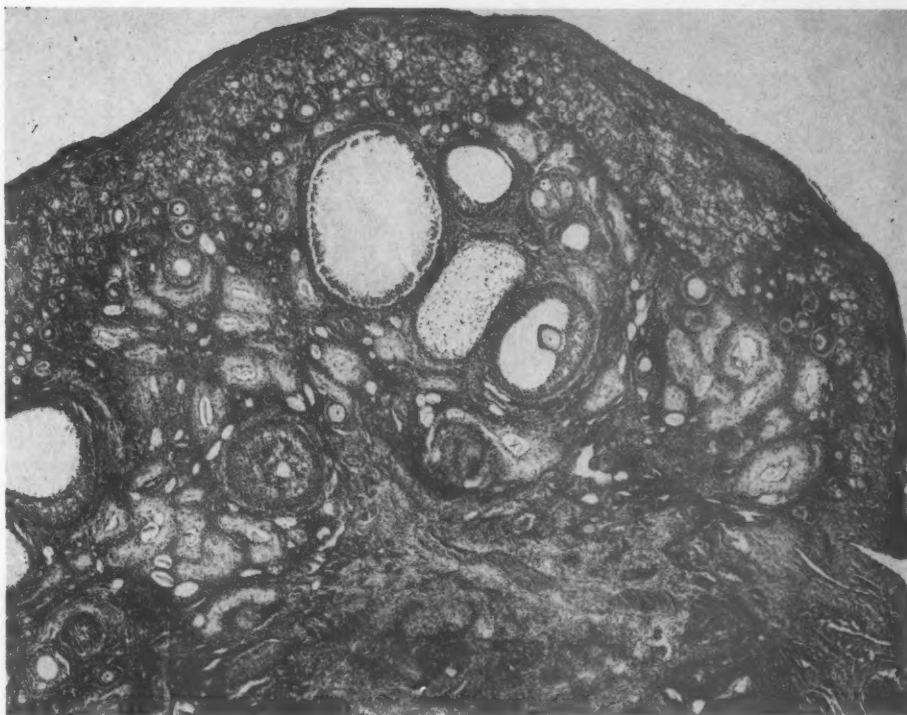


Fig. 1. Normal ovary of *Macacus mulatta*. ($\times 25$.)



Fig. 2. Monkey T-1. Left ovary removed one year after total hysterectomy. ($\times 25$.)

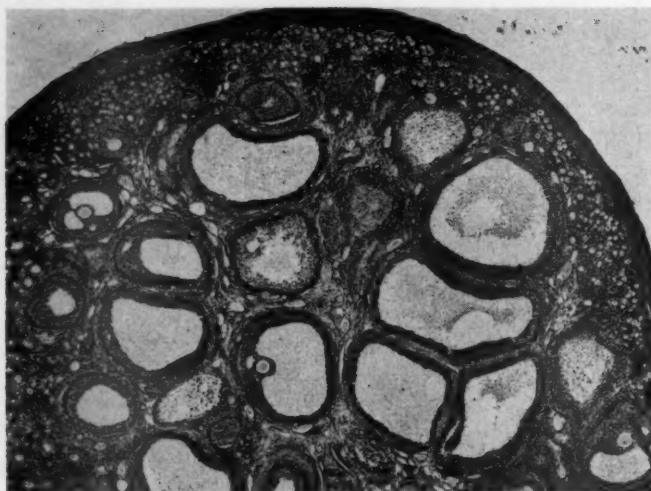


Fig. 3. Monkey T-1. Another area of left ovary one year after total hysterectomy. ($\times 25$; reduced $\%$.)

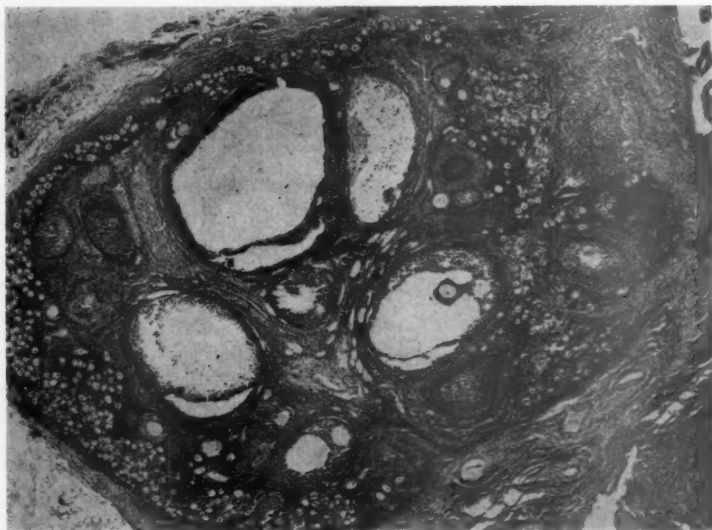


Fig. 4. Monkey T-1. Right ovary 2 years after total hysterectomy and one year after left salpingo-oophorectomy. ($\times 25$; reduced $\%$.)

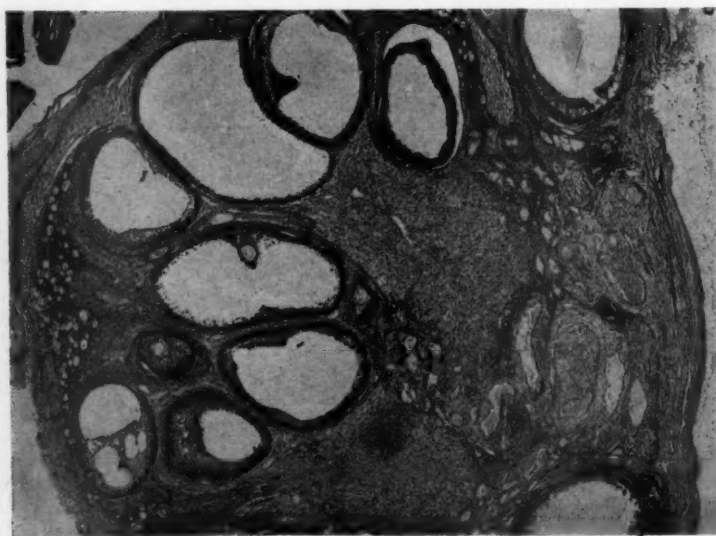


Fig. 5. Monkey T-1. Right ovary—same as that shown in Fig. 4. ($\times 25$; reduced $\%$.)

do not have cyclic menstruation. Little work on this problem has been done in primates. Van Wagenen and Catchpole⁵ performed subtotal hysterectomies on rhesus monkeys 4 to 6 days after term delivery and later found a normal resumption of ovarian activity as evidenced by study of vaginal desquamation. Mandl and Burger⁶ used an ape and 5 rhesus monkeys. Following subtotal hysterectomy, they found follicles in all stages of development and also corpora lutea. There may have been fewer primordial follicles in the ape. Jones and TeLinde⁷ found no change in vaginal estrus cycle or in sex swelling of the rhesus monkey following hysterectomy, while Burford and Diddle⁸ noted no degenerative process in the ovary of 5 *Macacus rhesus* monkeys subjected to hysterectomy.

This study was undertaken because of a renewed interest in the fate of the ovary following hysterectomy and in postmenopausal ovarian function. Six mature female animals were used. Five were *Macacus irus* and one *Macacus rhesus*. Fig. 1 shows a normal rhesus ovary. The *Macacus irus* (Java monkey) is quite similar to the rhesus. It is slightly smaller and has cyclic menstruation at about 28 day intervals. The organs of reproduction are anatomically and histologically identical. After the animals had been allowed to adjust to their new environment and cyclic menstruation observed, 24 hour urine samples, usually 4, were collected at weekly intervals for FSH determination. Follicle stimulating hormone (FSH) determinations were done by means of the filter paper electrophoresis method reported by Stran and Jones.⁹ Laparotomy was then performed with careful observation and measurement of the ovaries. Various operative procedures were then carried out. The animal was followed by further laparotomies, FSH determinations, and ultimately by autopsy.

Monkey T-1. *Macacus irus*. A total abdominal hysterectomy was performed on June 6, 1956. The ovaries appeared normal but no corpora lutea were seen. Approximately one year later

on June 4, 1957, laparotomy was repeated. The ovaries were approximately the same size as before. No fresh corpora lutea were seen. There were a few adhesions. The left ovary was removed. Sections of this showed many follicles at all stages of development and old luteal material (Figs. 2 and 3).

On May 27, 1958, about 2 years after hysterectomy, the animal was killed with intravenous ether. Aside from a few adhesions in the pelvis, all organs were grossly normal. The remaining ovary was almost double its former size and contained an 8 mm. recent corpus luteum. The ovarian vessels were of normal size. The adrenal and pituitary glands as well as all other organs, were normal. Histology sections of the ovary (Figs. 4 and 5) showed follicles in all stages of maturation with a recent corpus luteum. The Fallopian tube had normal tall epithelium lining its lumen, and the vaginal mucosa showed good cornification.

The adrenal and pituitary glands showed no alteration and all other organs were histologically normal.

The FSH determination prior to hysterectomy in this animal was negative on four occasions. Prior to operation in the spring of 1957, 4 of 5 FSH determinations were positive while one year later prior to autopsy 4 of 5 weekly determinations were again positive.

Monkey T-2. *Macacus irus*. This animal had the left tube and uteroovarian ligament sectioned and ligated on April 17, 1956. The internal genitals appeared normal. Old corpora lutea but no fresh ones were seen. On June 12, 1956, the animal was explored again. The ovaries were unchanged in size or appearance except for a 4 mm. corpus luteum in the left ovary. No biopsy specimens were taken.

Cyclic menstruation continued except for the usual summer amenorrhea, and on April 9, 1957, the monkey was again explored. The ovaries and uterus all appeared normal.

The right ovary contained a 6 mm. fresh corpus luteum. The left tube and ovary were removed. The former was normal histologically. The ovary (Fig. 6) contained many follicles in all stages and a degenerating corpus luteum. Normal menses continued and the animal died Feb. 10, 1958. The remaining right ovary was approximately the same size as in prior operations. The uterus, tube, and vagina were also normal. The adrenal glands were perhaps slightly smaller than average but within normal limits.



Fig. 6. Monkey T-2. Left ovary one year after section of left tube and utero-ovarian ligament. ($\times 25$.)

No other pertinent findings were noted. Histological study of the autopsy material showed the pancreas, liver, pituitary, and other organs to be normal. The adrenal glands were quite normal except for slightly more pigmentation in the cells of the zona reticularis. The uterine endometrium showed an early secretory pattern. The ovary (Fig. 7) contained a corpus luteum, many developing follicles, and normal stroma. The vaginal epithelium had good keratinization.

FSH determination in 1956 prior to the first operation showed one positive and three negative results. Three of four FSH determinations prior to laparotomy in April, 1957, were positive.

Monkey T-3. *Macacus irus*. A right salpingectomy and left Pomeroy tubal ligation were done on March 27, 1956, at Day 19. Two months later at laparotomy the ovaries appeared to be normal. At the first operation, the right ovary was noted to contain a corpus luteum. This was no longer visible, and the left ovary now contained a corpus luteum. Normal menses continued, and on April 9, 1957, the animal was explored again and the left tube and ovary removed. Both ovaries were the same size as at both prior laparotomies and the left ovary contained a fresh corpus luteum. Sections of this ovary (Fig. 8) confirmed the presence of the

fresh corpus luteum. In addition, older lutein tissue was present as well as many follicles, both immature and developing. Normal cyclic menstruation continued. The monkey was killed on April 8, 1958 (Day 2), approximately 2 years after the first laparotomy. The remaining right ovary was approximately the same size as at the preceding operation and appeared to be normal. The ovarian vessels were somewhat larger than average. The uterus was normal in size and was somewhat congested. The adrenals were slightly smaller than average and the other organs appeared to be normal. Histological study of the ovary (Fig. 9) revealed a fresh regressing corpus luteum compatible with Day 2. Old lutein tissue and numerous follicles in all stages of maturation were present. The endometrium was of a secretory menstruation pattern (Fig. 10). The vagina showed good cornification. The adrenal glands, liver, pancreas, and pituitary were histologically normal.

In February, 1956, four FSH determinations were negative while one year later one determination was positive and one negative. Two specimens were unsatisfactory. In February and March, 1958, three of five determinations were positive.

Monkey T-4. *Macacus irus*. A subtotal hyster-

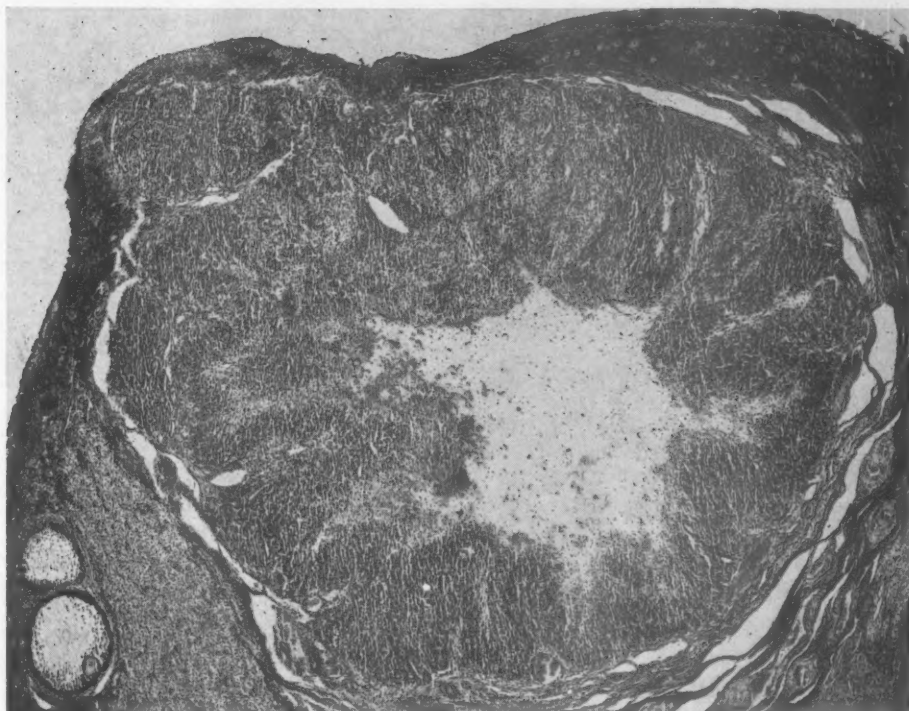


Fig. 7. Monkey T-2. Right ovary—taken one year after Fig. 6. ($\times 25$.)

ectomy was done on Day 24 on Feb. 16, 1956. The ovaries appeared to be normal, the right containing a corpus luteum corresponding in characteristics to the menstrual date. Laparotomy was repeated 2 months later. The only residual of the corpus luteum (Fig. 11) in the right ovary was a tiny fleck of yellowish pigmentation, and the left ovary (Fig. 12) now contained a fresh corpus luteum. Both ovaries were unchanged in regard to size, biopsy specimens were obtained. Sections showed numerous follicles and a fresh corpus luteum.

In January, 1957, the animal died of pneumonitis. At autopsy the ovaries were found to be somewhat reduced in size. The ovarian vessels were smaller than average and no accessory blood supply was found. The cervical stump appeared to be normal as were the adrenal glands, pancreas, kidneys, and pituitary. The liver was somewhat congested. Histology sections of the ovaries showed relatively fresh corpora lutea (Fig. 13), one of which was being vascularized. Also many follicles in varying stages of maturation were present. The vaginal and cervical squamous epithelium showed good cornification. A small bit of nonsecretory proliferative endometrium was present in the endocervical canal. In the adrenal glands there was slightly

increased pigmentation in the zona reticularis. The hypophysis was normal. FSH determinations were performed only prior to initial operation when two of four determinations were positive.

Monkey T-5. *Macacus irus*. On Jan. 24, 1956, a total hysterectomy was performed on Day 23 with removal of a normal mature uterus. The left ovary contained a 6 mm. cystic corpus luteum. Laparotomy was repeated on April 10, 1956. The ovaries were of the same size. No cysts or corpora lutea were seen. A biopsy specimen was taken from the site of the corpus luteum noted in the left ovary at the previous operation (Fig. 14). This showed numerous developing follicles and old theca lutein cells present.

On Feb. 12, 1957, the animal was explored again. The ovaries were unchanged in regard to size and appeared to be normal with a corpus luteum in the right. This ovary (Fig. 15) was removed and appeared to be quite normal with a normal number of follicles in varying degrees of maturation in addition to the corpus luteum noted grossly. One year later on Feb. 25, 1958, the animal was killed. The left ovary showed a moderate increase in size but appeared to be entirely normal and free from cystic changes. Histology sections (Fig. 16) showed numerous

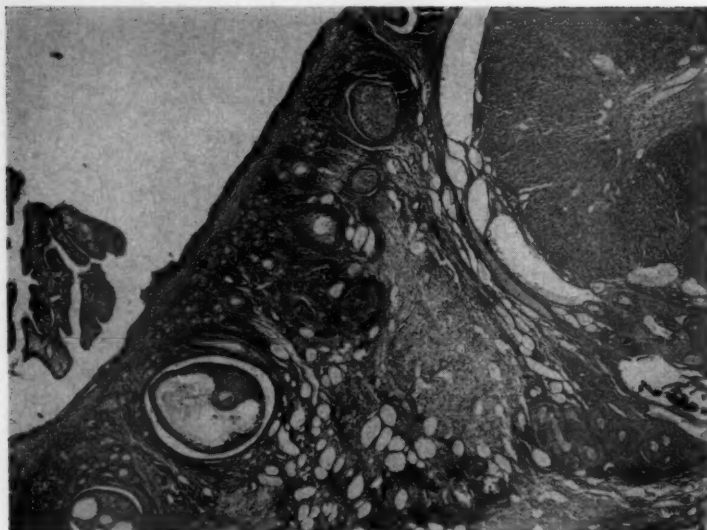


Fig. 8. Monkey T-3. Left ovary one year after right salpingectomy and left Pomeroy tubal ligation. ($\times 25$; reduced %.)



Fig. 9. Monkey T-3. Right ovary 2 years after right salpingectomy and one year after left salpingo-oophorectomy. ($\times 25$; reduced %.)

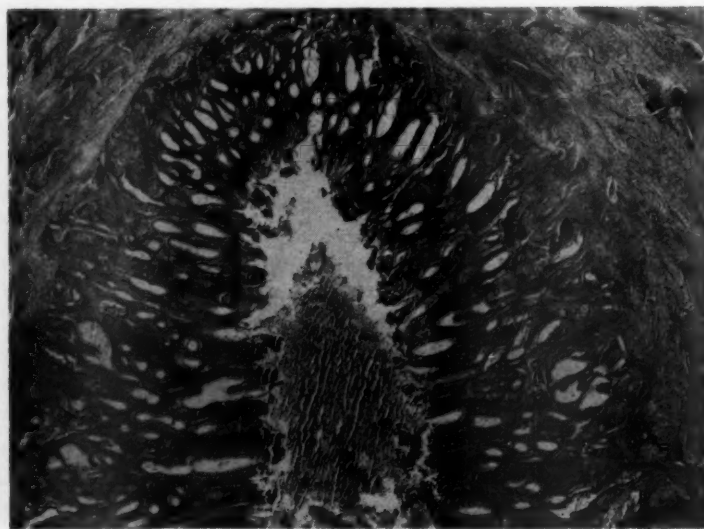
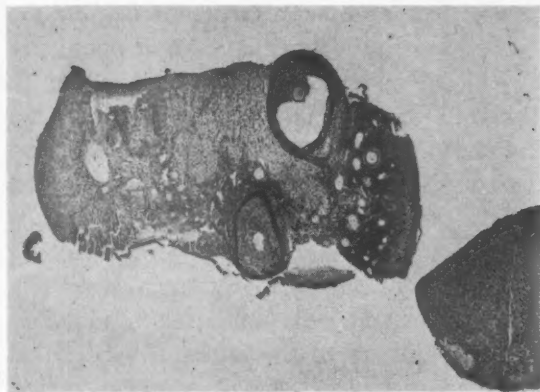
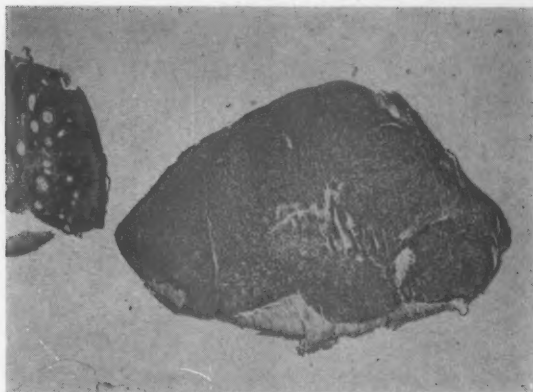


Fig. 10. Monkey T-3. Endometrium on Day 2—taken at time of Fig. 9. ($\times 25$; reduced %.)



11

Fig. 11. Monkey T-4. Biopsy of right ovary at site occupied by corpus luteum at time of subtotal hysterectomy 2 months previously. ($\times 25$; reduced $\frac{1}{4}$.)



12

Fig. 12. Monkey T-4. Left ovary biopsied at time of Fig. 11. ($\times 25$; reduced $\frac{1}{4}$.)

follicles in all degrees of maturation plus old lutein material. The vaginal epithelium showed good keratinization. All other organs were grossly and microscopically normal.

FSH determinations prior to operation showed two of four to be positive, while one year later four were positive, one equivocal, and two negative. A series of determinations in 1958 showed two to be positive, one probably positive, two equivocal, and one negative.

Monkey 841. *Macacus mulatta*. This animal had a total hysterectomy with a 95 day intra-uterine pregnancy in situ on Feb. 14, 1956. This was done as part of an investigation by Dr. Elizabeth Ramsey of the Department of Embryology, Carnegie Institution of Washington. The ovaries were normal. There were multiple adhesions from prior laparotomies. On May 1, 1956, another laparotomy was performed. Aside from the adhesions, the ovaries appeared to be

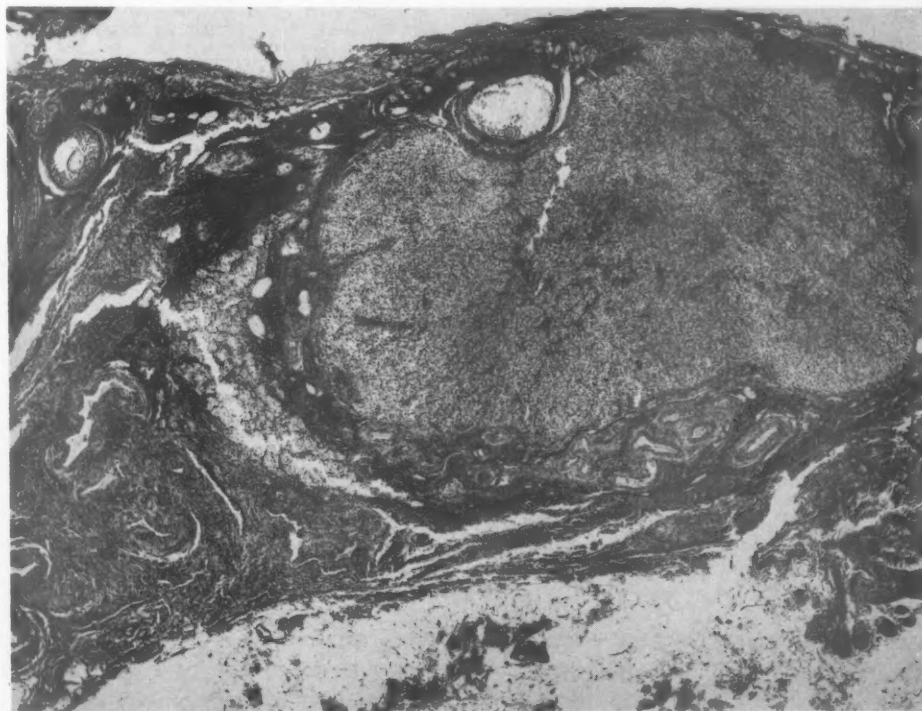


Fig. 13. Monkey T-4. Right ovary removed 11 months after subtotal hysterectomy. ($\times 25$.)



Fig. 14. Monkey T-5. Biopsy of left ovary at site occupied by corpus luteum at time of total hysterectomy 11 weeks previously. ($\times 25$; reduced 2%.)

normal and were approximately the same size as before. Biopsies were taken from each (Figs. 17 and 18), section of which showed normal follicular apparatus and also a regressing corpus luteum.

Another exploratory laparotomy was carried out on June 4, 1957. The ovaries were unchanged in size or appearance and the left was removed (Fig. 19), again showing normal ovarian stroma, follicles, and a regressing corpus luteum. On Feb. 25, 1958, the animal was killed. The right ovarian vessels were large, and the ovary showed considerable compensatory hypertrophy but seemed to be normal otherwise.

The ovary (Fig. 20) histologically showed a vascularized corpus luteum, normal stroma, and follicles. There was a moderate degree of periophoritis and salpingitis, probably from the silk, which was demonstrable. The vaginal epithelium was thick with a small area of secretory endometriosis in the vault. The adrenal glands were normal except for moderate pigmentation of the zona reticularis. The hypophysis and other organs were normal grossly and microscopically.

FSH determinations in the spring of 1957 were positive on all four specimens while in 1958 four specimens were positive, one equivocal, and one negative. Preoperative determinations were not made because of the normal pregnancy.

Comment

In these 6 animals a variety of primary procedures were performed, including tubal ligation, salpingectomy, section of tube and uteroovarian ligament, subtotal hysterectomy and total hysterectomy. Four had 2 ad-

ditional laparotomies prior to autopsy and the other 2 animals were explored only once after the initial operation. The intention was to perform the initial operation during the luteal phase of the cycle to observe the presence or absence of the corpus luteum and then to re-examine the ovary about 2 months later to evaluate persistence or regression of the corpus luteum. Laparotomy was usually performed about one year after the first operation and then the animal was killed after another year. An observation period of 2 years' duration should be sufficient to observe any changes in the ovary, be they vascular, neurogenic, or hormonal, while further prolongation of the period of observation might lead to ovarian changes due to aging since in no case was the chronological age of the animal known. That 2 animals died of intercurrent disease was unfortunate but not unexpected since this is one of the chronic problems in animal experimentation. The observations made on these animals, we feel, are still valid since the periods of observation were 11 and 22 months.

Although the operative procedures varied somewhat, the ovarian findings were similar and bore no relation to the procedure. While both ovaries remained in place there was no change in their over-all dimension in all the animals except one. This animal (T-4) died of pneumonitis after 11 months, and the ovaries were appreciably smaller than at either prior measurement. Despite the apparent gross atrophy, these ovaries showed evidence of good function with numerous follicles and even corpora lutea. In this animal all ovarian vessels were also smaller than average, and it is possible that the over-all reduction in blood flow following hysterectomy caused some decrease in ovarian volume but not in function, nor did it lead to cystic change usually attributed to chronic vascular insufficiency. In 5 animals one ovary was removed at a later date for study and it is noteworthy that in 4 the remaining gonad underwent a significant degree of hypertrophy. In the other animal (T-2) the ovary was un-

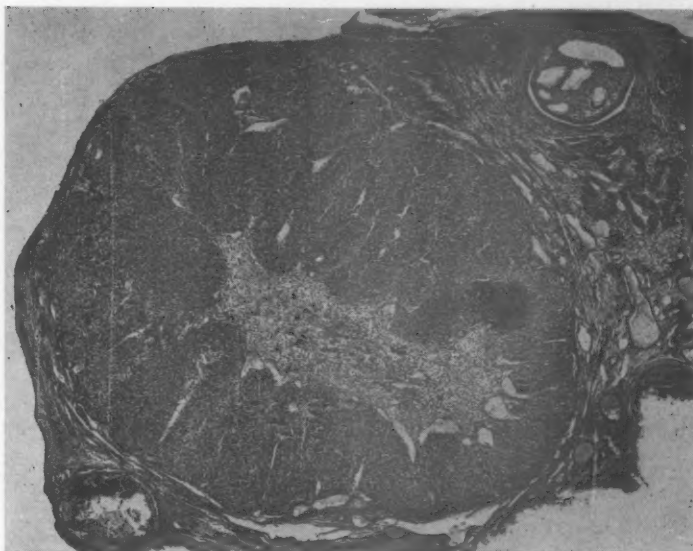


Fig. 15. Monkey T-5. Right ovary removed 13 months after total hysterectomy. ($\times 25$; reduced $\frac{2}{3}$.)

changed in regard to size even though the ovarian vessels were of good caliber. This ovary again gave evidence of normal functional activity with a corpus luteum being present, matching a secretory endometrial pattern. From these observations on the ovarian size, it would appear that removal of the uterus, severance of the uteroovarian vascular and nerve pathways, salpingectomy, and tubal ligation caused no significant change in ovarian size and, furthermore, that the gonad remaining after unilateral oophorectomy at a later date is usually

capable of undergoing compensatory hypertrophy.

Among the effects on the ovary attributed to uterine or adnexal operations is persistence of the corpus luteum. Of the 5 non-pregnant animals in this series, the ovaries of 3 contained fresh corpora lutea at the time of the initial operation. When the ovaries were inspected about 8 weeks later, the original corpus luteum had regressed in each instance, and 2 of these animals showed a fresh corpus luteum in the opposite ovary. Thus, there was no evidence of

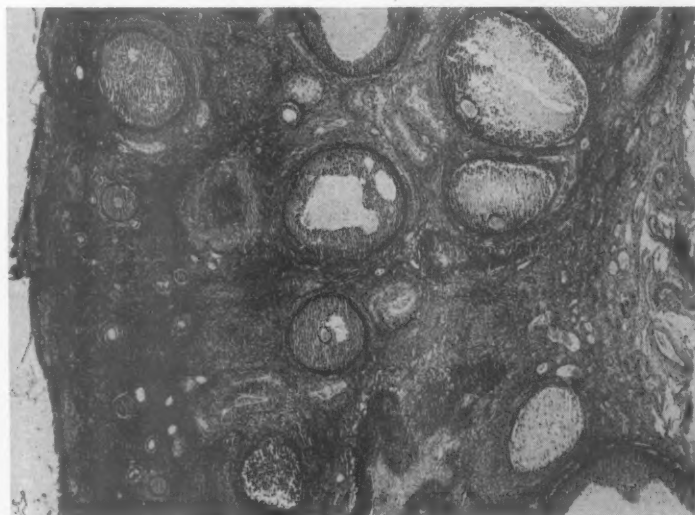


Fig. 16. Monkey T-5. Left ovary 25 months after total hysterectomy and one year after right salpingo-oophorectomy. ($\times 25$; reduced $\frac{2}{3}$.)

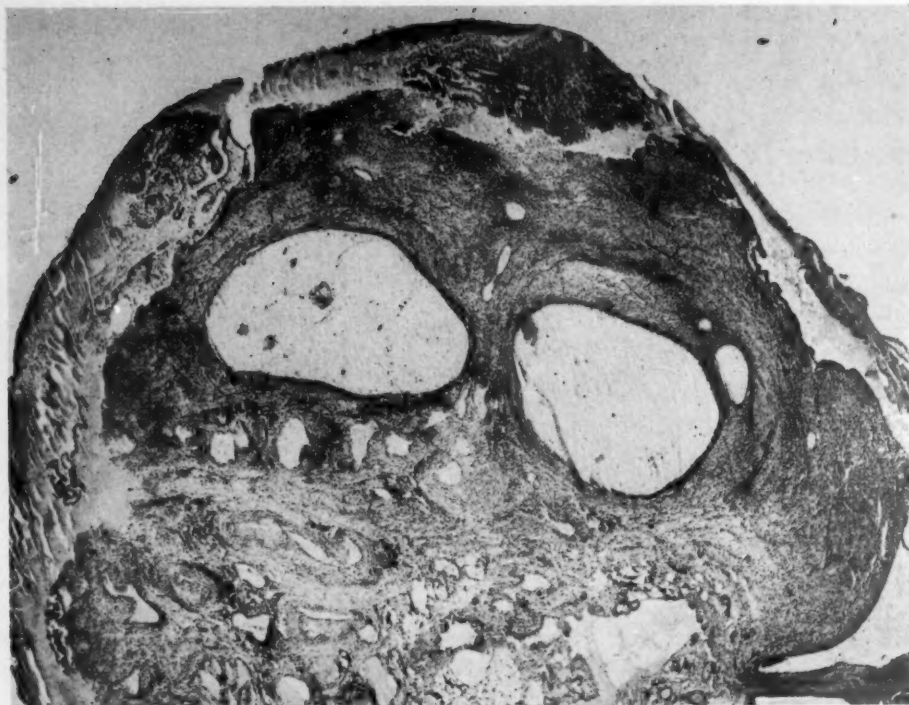


Fig. 17. Monkey 841. Right ovarian biopsy 11 weeks after total hysterectomy. (×25.)

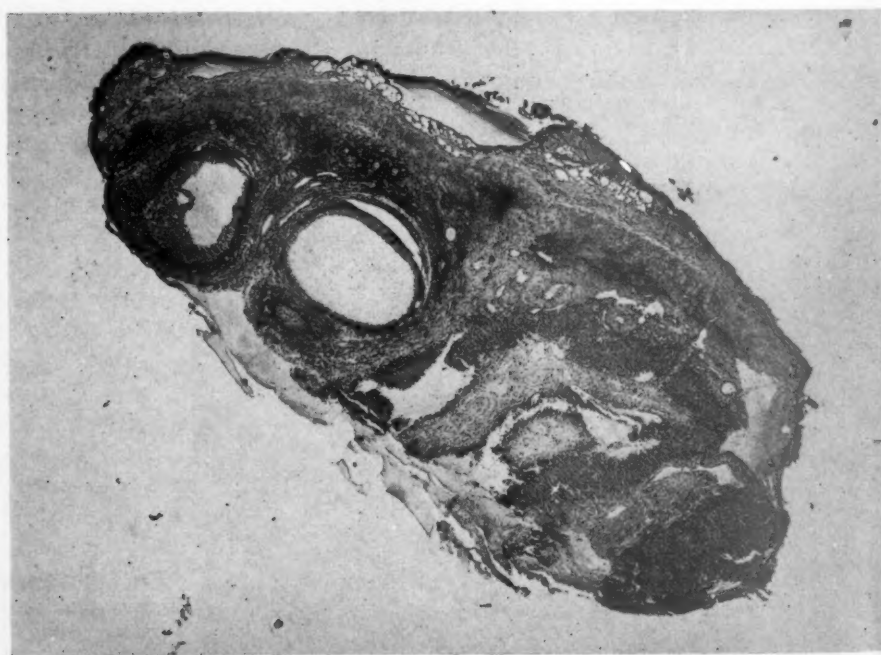


Fig. 18. Monkey 841. Left ovarian biopsy 11 weeks after total hysterectomy. (×25.)

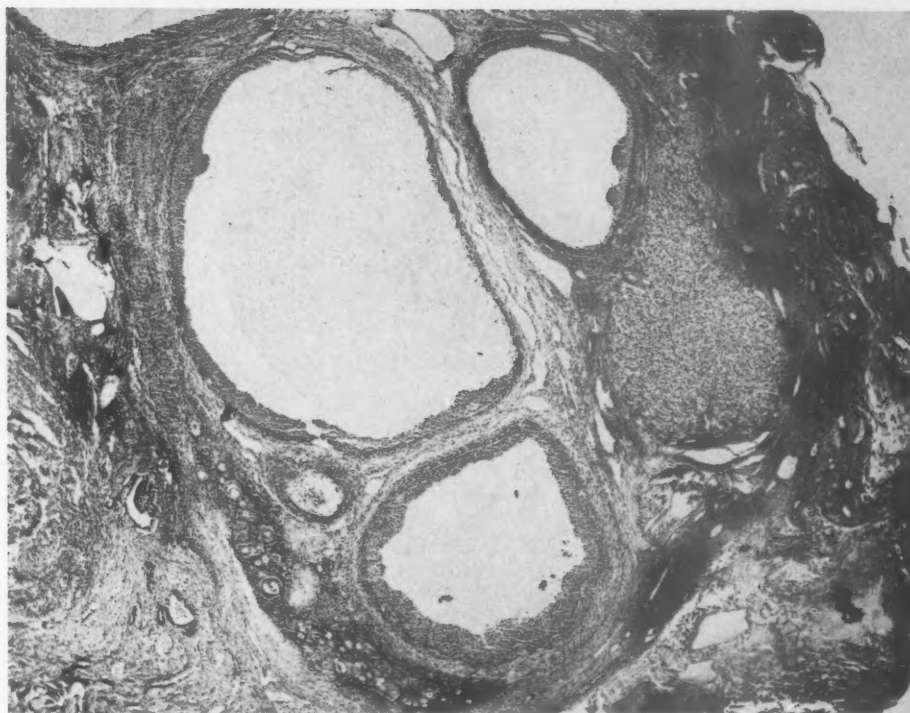


Fig. 19. Monkey 841. Left ovary 16 months after total hysterectomy. ($\times 25$.)

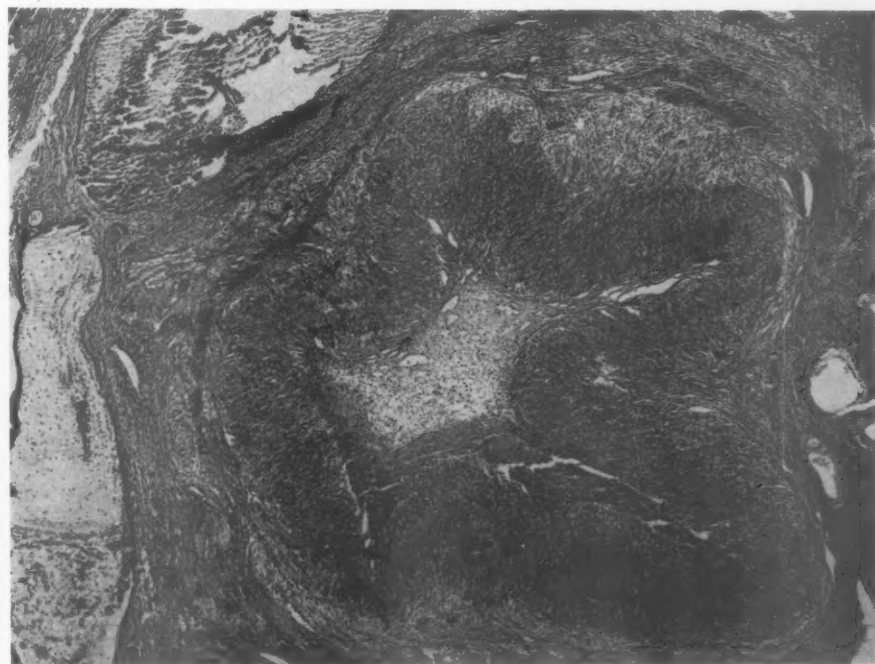


Fig. 20. Monkey 841. Right ovary 2 years after total hysterectomy and 8 months after left salpingo-oophorectomy. ($\times 25$.)

persistence of the corpus luteum in the Java monkey or the pseudopregnancy effect as noted in the rabbit.

The presence of a mature corpus luteum is generally conceded to be evidence of ovulation. In these animals, the ovaries were not inspected with sufficient frequency to determine the regularity of ovulation. The animals with retained uteri all had regular cyclic bleeding which, of course, is not necessarily an index of frequency of ovulation but merely is substantial evidence of continued ovarian function. It is clear, however, that ovulation did occur in all these animals since corpora lutea were observed in every monkey at some time following the primary operation.

Van Wagenen and Catchpole⁵ concluded that puerperal subtotal hysterectomy on *Macacus mulatta* did not interfere with the resumption of ovarian activity. Their conclusions were reached not by laparotomy but by study of vaginal desquamation. We were fortunate to operate on one pregnant animal (No. 841) and can confirm the study of Van Wagenen and Catchpole with the observation of a regressing corpus luteum 10 weeks later. Corpora lutea were also observed in this animal 16 and 24 months later, indicating continuance of ovarian function.

The effect of pelvic operation on the follicular apparatus is more difficult to assess. Increased follicular atresia, degeneration, and cystic change have been attributed to hysterectomy or adnexal operations. In regard to these changes, in no case did the ovary become cystic; nor were there even abnormally large follicles. Polycystic change also was not noted. The ratio of primordial, mature, and atretic follicles in a given ovary to a great degree will be dependent upon the age of the animal so that a compilation of numbers of this or that type of follicle is meaningless. In our animals many follicles exhibiting all degrees of maturation and atresia can be found, and no derangement of the follicular apparatus can be noted. Ova are seen and the granulosa and thecal layers appear quite normal.

The interstitial body consisting of a mass of large vacuolated interstitial cells replacing the normal ovarian stroma, which has been reported in the rabbit by Tenny,⁴ has never been described in primates. One would not expect, therefore, to find such stromal changes even after hysterectomy in the monkey but we could detect no change in morphology, density, or staining characteristics of the ovarian stromal cells in our animals.

In the rabbit, according to Tenny,⁴ the adrenal glands hypertrophy after bilateral oophorectomy. He further reports a similar change following total hysterectomy or tubal ligation. The hypertrophy is due to a thickening of the zona fasciculata and the appearance of large clear cells with reticulated cytoplasm in the zona reticularis. The degree of adrenal hypertrophy is said to parallel the extent of ovarian change in the rabbit. This is also true in the monkey. We have observed no change in either the ovary or adrenal in this animal. The adrenal glands, regardless of the type of pelvic procedure, were of normal size or, if anything, slightly smaller than average. The adrenal glands of 3 animals showed moderate pigmentation of the zona reticularis, but there was no alteration of the size of the various zones. The hypophysis of all these animals were also studied with hematoxylin and eosin stain and the Mann stain. These glands all were of uniform size and histological appearance and no abnormalities were noted.

An attempt has been made to evaluate the urinary excretion of the follicle stimulating hormone before and after operations on the pelvic organs of the monkey. Little work has been done on FSH excretion in either the rhesus or Java monkey so preoperative baseline studies were done in the 5 nonpregnant animals. There were technical problems in collecting 24 hour urine specimens in these animals. In 2 animals four consecutive weekly specimens were negative for FSH; one had one positive specimen and 2, two positive specimens. Four animals had two series of FSH determina-

tions postoperatively and one series was done in another animal. It is difficult to discern any particular pattern in these determinations, but one conclusion can be reached, namely, that in no animal was the FSH excretion less after operation than before. Often the FSH excretion was increased somewhat in the postoperative studies but the pattern was erratic and bore no relation to the type of operation performed. The results of the FSH excretion studies were reviewed by Dr. G. E. Seegar Jones, who concluded that there is no evidence that the ovaries had ceased to function.

A further index of continual ovarian function at least of estrogenic activity can be found in the vaginal epithelium. No animal in this series showed any evidence of thinning or atrophy following the operative procedures but, on the contrary, the findings were consistent with continued estrogenic activity with thick vaginal mucosa and continued keratinization. This correlates well with studies on women after hysterectomy. Bancroft-Livingston,¹⁰ in his study of vaginal smears following hysterectomy, concluded that ovarian tissue preserved at the time of operation continued to function for a considerable time and that the onset of ovarian failure was not hastened by hysterectomy. McCall, Keaty, and Thompson,¹¹ in a study of ovaries retained after radical operation for cervical carcinoma, also found continued estrogenic effect by vaginal cytology.

Conclusions

The changes in the ovary following hysterectomy or adnexal operations in the rabbit as reported by Tenny, Parker, and Robbins,⁴ consisting of follicle degeneration and development of the interstitial body, indications of premature aging, have not been confirmed in cyclicly menstruating primates subjected to similar procedures. In the rhesus and Java monkeys ovarian morphology is unchanged and ovarian function appears to continue without obvious alteration and without apparent senescence. When one ovary is removed at a later date, the re-

maining ovary is usually capable of compensatory hypertrophy. Follicles can be found in all stages of maturation and atresia, and corpora lutea develop and recede normally. The ovarian stroma is unchanged. No gross or morphological changes have been observed in the hypophysis or adrenal glands of these animals, and the urinary excretion of FSH appears to be essentially unchanged.

It is difficult to resolve the obviously conflicting observations in the primate and the rabbit or for that matter the guinea pig or rat. These 3 animals, of course, do not have cyclic menstruation, and their menstrual physiology is quite different from that of cyclicly menstruating primates or women. Furthermore, there is very little anatomical similarity of the pelvic organs so that, while operations are performed which on the surface would appear to be quite comparable, the effects of these procedures may in no way be similar and the alteration of the blood flow, innervation, or even endocrine function may differ greatly.

Extreme care should be used in any attempt to apply the results of animal experimentation to humans. If any findings are likely to be valid in a study of reproductive physiology, the rhesus or Java monkey, both of which have regular cyclic menstruation and reasonably similar genital anatomy, should be animals of choice for such an undertaking. Clinically there has been little reason to suspect gross aberrations in ovarian physiology following hysterectomy in women, and we were surprised to find reports of such drastic changes in some experimental animals. There is little opportunity or reason to inspect or remove the ovaries remaining after hysterectomy in most women. Work by Bancroft-Livingston,¹⁰ with vaginal smears as an index of ovarian activity, indicates that hysterectomy with ovarian conservation in women does nothing to hasten the onset of ovarian failure and that the ovarian tissue continues to function for a considerable period of time with the frequency of ovulatory cycles of the same order of magnitude had the uterus

not been removed. The data obtained from the monkeys do not allow us to reach such broad conclusions, but there is evidence of continued ovulation and apparently unimpaired ovarian function for periods as long as 2 years after hysterectomy or other adnexal operations in the Java and rhesus monkeys.

As stated before, the drawing of clinical conclusion on the human based upon laboratory experiments on lower animals is somewhat risky. However, we can at least say that these experiments do not afford any basis to support the indiscriminate removal of ovaries in younger women during a hysterectomy.

Summary

1. The effect of pelvic operations on the ovaries and their function has been difficult to assess because of markedly divergent find-

ings in a variety of experimental animals.

2. Six monkeys, 5 *Macacus irus* and one *Macacus mulatta*, were subjected to tubal ligation, salpingectomy, section of tube and uteroovarian ligament, subtotal hysterectomy, and total hysterectomy and were followed by laparotomies, FSH determinations, and, ultimately, autopsy.

3. No evidence of impairment of ovarian function was noted as evidenced by derangement of follicular or corpus luteum development, maturation, or regression, nor were there any detectable ovarian stromal changes.

We wish to express our gratitude to the Department of Embryology, Carnegie Institution of Washington, and its Director, Dr. James D. Ebert, and staff for the use of their facilities and assistance. FSH determinations were done through the courtesy of Dr. G. E. Seegar Jones and her laboratory.

REFERENCES

1. Grogan, Richard H., and Duncan, Christopher J.: AM. J. OBST. & GYNEC. 70: 1277, 1955.
2. Grammatikati, J.: Centralb. f. Gynäk. 13: 105, 1889.
3. Reynolds, S. M. R.: Physiology of the Uterus, New York, 1949, Paul B. Hoeber, Inc., chap. 35, p. 503.
4. Tenny, B., Parker, F., Jr., and Robbins, S. L.: AM. J. OBST. & GYNEC. 70: 889, 1955.
5. Van Wagenen, G., and Catchpole, H. R.: Proc. Soc. Exper. Biol. & Med. 46: 580, 1941.
6. Mandl, L., and Burger, O.: Die Biologische Bedeutung der Eierstöcke nach Entfernung der Gebärmutter, Leipzig u. Wein, 1904, Franz Deuticke.
7. Jones, G. E. S., and Telinde, R. W.: AM. J. OBST. & GYNEC. 41: 682, 1941.
8. Burford, T. H., and Diddle, A. W.: Surg. Gynec. & Obst. 62: 701, 1936.
9. Stran, H. M., and Jones, G. E. Seegar: Bull. Johns Hopkins Hosp. 95: 162, 1954.
10. Bancroft-Livingston, George: J. Obst. & Gynaec. Brit. Emp. 61: 628, 1954.
11. McCall, M. L., Keaty, E. C., and Thompson, J. D.: AM. J. OBST. & GYNEC. 75: 590, 1958.

Discussion

DR. RONALD R. GREENE, Chicago, Illinois. It is difficult to discuss this extremely interesting paper by Dr. Telinde and Dr. Wharton since their findings agree so well with my own preconceived notions on this subject.

In their introduction they stress the fact that the literature on the effects of hysterectomy on the ovary in the experimental animal is very confusing. It is. At one time Brooks Ranney, Ben Peckham, and I studied the effects of hysterectomy on the ovary in the rat—done when the animal was immature, mature, or pregnant. When compared with adequate controls there were no

resulting abnormalities of ovarian development, function, or morphology. As a result of this study, I am moderately familiar with the literature on this subject. I would not go so far as the authors in admitting that changes in the ovary following hysterectomy in the rabbit, rat, and guinea pig have been found uniformly by various observers.

I heartily agree that findings in the menstruating primates would more likely be applicable to the human than those from nonmenstruating animals, although it should be pointed out that the rat and guinea pig do have regular ovulatory cycles. In the rat the cycle is so short

that it is doubtful that the corpus luteum functions to any extent—if at all. In the guinea pig the corpus luteum does function and with cessation of its function, according to Papanicolaou, there is a desquamation of the surface endometrial epithelium which is not associated with bleeding.

I wonder if it is clear why 2 of the animals in this present series were subjected to tubal operations only. In one the left tube and uteroovarian ligament were sectioned and ligated. In the other a right salpingectomy and a left tubal ligation were performed. Tenney, Parker, and Robbins have claimed that follicular degeneration and development of the interstitial body occurs in the rabbit's ovary following hysterectomy. Astonishingly enough, it is also supposed to occur with tubal ligation without hysterectomy and, even more astonishingly, it is supposed to occur in both ovaries when only one tube is ligated. Obviously this did not happen in the monkey.

I believe that Dr. TeLinde and Dr. Wharton have demonstrated that, in the monkey, hysterectomy causes no changes in the morphology and function of the ovary. Also they have demonstrated that salpingectomy and tubal ligation similarly have no effect. I cannot prove it, but I am morally certain that these findings apply to another primate—the human.

DR. SOMERS H. STURGIS, Boston, Massachusetts. The decision to take out or leave behind the ovaries during a routine hysterectomy is of important concern to all in our specialty. The present paper by Drs. TeLinde and Wharton provides appropriate information to aid us in such a decision.

There are two fundamental aspects to this problem, and they may be stated in this way: First, except for childbearing, are normal ovaries of any value at all or do they merely constitute a threat to the life and health of the individual woman involved and thus should be removed at any time under any circumstances that prohibit future pregnancy? After answering this basic question, we must move on to the second, with which the present report is particularly concerned: Does hysterectomy influence the function of retained ovaries so that they become more of a threat to life or health than when the uterus was still in place?

The answer to the first question involves one's personal philosophy. If it is one's belief that ovaries, except for childbearing, represent nothing

but a threat and add nothing whatever that cannot easily be replaced with pills, then out they should come at any opportunity that contraindicates another gestation.

Such contraindications should include (a) women who for other reasons must not become pregnant, (b) women who are satisfied with the completeness of their families, or (c) even if not satisfied, women whose advancing age or husbands' infertility or other reasons suggest they would not be able to become pregnant. I doubt if this would be a majority opinion of those present today. I do not believe that members of this society would care to go on record in favor of urging all surgeons to include castration as part of any exploratory laparotomy at any age on the basis of one of the three reasons listed above.

Strong support for bilateral oophorectomy was found 5 years ago by Grogan and Duncan, in their appraisal of 635 women undergoing hysterectomy at 39 years or under. Thirty-eight per cent of the women in this series were castrated. The authors concluded that "the interests of the patient are best served by bilateral oophorectomy at time of routine hysterectomy." We must infer that their answer to the first basic question would be that, except for childbearing, ovaries are no good and should always be ablated.

Those of us who are inclined to reject such a sweeping conclusion must then face the second basic question. Does removal of the uterus make the ovaries more of a threat than they were when the uterus was in place?

Grogan and Duncan make no attempts to answer this difficult problem. They state that 33 per cent of the 391 women with retained ovaries got into some sort of postoperative trouble compared with only 13 per cent after bilateral oophorectomy. These included ovarian endometriosis, adhesions of bowel to ovary, simple cysts, and so on, and 20 women, or 5 per cent, needed subsequent laparotomy. No ovarian malignancy was encountered in this group so that the incidence of neoplastic change in the retained ovary was less than 2 per 1,000. The authors did not contend that the ovarian complications occurred because of hysterectomy. Indeed, they felt that many of these 20 patients had incipient cysts, unrecognized endometriosis, and so on, at the time of hysterectomy, and would have had the same trouble if the uterus had not been removed.

One can only hope to answer this second question by experiments in laboratory animals.

Drs. TeLinde and Wharton, reviewing the provocative paper on the rabbit presented to this Society by Tenney and Parker 5 years ago, rightly point out that in the primate alone have we any right to form conclusions on the effect of hysterectomy on the ovaries with any hope of pertinence to the human female.

In the present report, these authors have intelligently used an admittedly small number of experimental animals to the fullest extent of operative maneuvers. They have been able to extract therefrom factual data of much help in this problem. These data tend to establish that, in cyclic, menstruating primates, contrary to Tenney and Parker's findings in rabbits, the removal of the uterus or the ligation or removal of a tube or one ovary does not limit, hinder, or inhibit normal ovulation from the retained ovarian tissue for at least 2 years. It is too bad that quantitative FSH determinations were not available.

As TeLinde notes, "there are technical problems in collecting 24 hour urine specimens from these animals." The method used was a qualitative one, and positive reactions were obtained both before and after operation. Quantitative tests, however, can be carried out on monkeys. Two years ago before this society, we included values on one of 6 monkeys tested before and after castration.¹ Special cages had to be constructed so that relatively clean urine, uncontaminated by feces, would drain into a container surrounded by dry ice over a 72 hour period. We found that before castration there was less than 2.5 mouse units per 24 hours according to the Albright technique we use routinely in our human material. In the monkey the level rose to positive for more than 10 units after castration in some of the animals.

If such values had been available in the present study and the FSH never rose to as much as 2.5 units per 24 hours posthysterectomy, this indeed would have been confirmation of the functional integrity of the gonads in Dr. TeLinde's monkeys, which was suggested by the normal morphology of the corpora lutea and estrogenic vaginal epithelium at time of sacrifice.

In conclusion, this paper once again forces us to come to a decision on a very basic question. For those who believe with me that the calculated risk of malignancy in normal ovaries does not justify their removal at any age or under any circumstance that contraindicates pregnancy and who believe, moreover, that the ovaries do a

better job providing hormones than the doctor's prescription pad, such studies as this lend support to the thesis that hysterectomy does not cause pathologic ovarian changes.

TeLinde and Wharton have given us such assurance when they conclude from their experiments that there is no basis to support the indiscriminate removal of ovaries in young women during a routine hysterectomy.

REFERENCE

1. Castellanos, H., and Sturgis, S. H.: *AM. J. OBST. & GYNEC.* 76: 1132, 1958.

DR. MILTON L. MCCALL, Pittsburgh, Pennsylvania. Drs. TeLinde and Wharton have added another very thorough study to the literature which tends to show the effect of ordinary hysterectomy on ovarian function. While the discussion so far has not been nearly so exciting, from the standpoint of vituperation and acrimonious debate, as that which is in the Transactions of this Society some 40 years ago when Harvard's Graves lined up against Johns Hopkins' Kelly, I certainly am not going to change the trend inasmuch as I agree fully with the conclusions of the essayists.

Although morphology studies are important, the functional aspects of this problem are also of great significance. In this connection, I would like to present some of the latest material upon the continuing study of young women with early squamous cell carcinoma of the cervix in whom ovaries were left in situ with the blood supply intact at the time of treatment with radical operation. This investigation has been going on since April, 1948, and a total of 55 consecutive patients between the ages of 22 and 39 years with Stage I or early Stage II lesions have been treated in this fashion. One has been lost to follow-up, and the results of follicle stimulating hormone studies on the remaining 54 are depicted in Fig. 1. It will be noted that there is only one patient who has a very high FSH value. Here, ovarian failure was brought about because a serous cystadenoma developed in the only remaining ovary. This was removed surgically 8 years after radical abdominal hysterectomy and is the only lesion of the ovary which has developed since the study was started. One of the women operated upon in 1951 by the abdominal route has a borderline FSH level but there is no other evidence of ovarian failure. The remaining

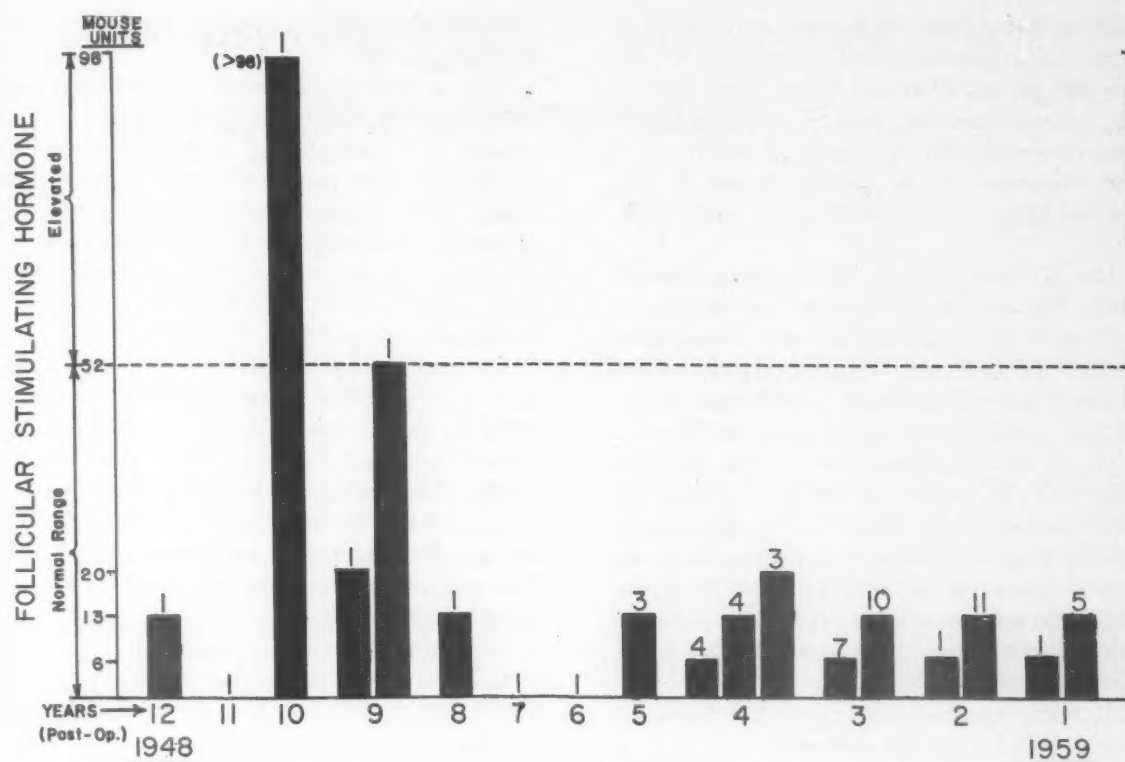


Fig. 1.

52 patients have normal FSH levels. These determinations have been multiple in many instances. In fact, as many as 10 FSH studies have been performed on some of the earlier patients over a period of years.

It seems evident, therefore, that ovaries continue to function normally even after radical hysterectomy, whether this be done abdominally or vaginally by the Schauta-Amreich technique. Certainly we should not worry ourselves concerning the function of ovaries after simple hysterectomy for benign conditions. It seems to me that studies of ovarian morphology and function as presented here should make us firm in the conviction that we should not hesitate to leave ovaries in situ and thereby add to our ability to perform more functional gynecological surgery than ever before.

DR. JOE V. MEIGS, Boston, Massachusetts. Years ago I operated upon the housekeeper in charge of my first office; she had previously been matron in one of the sanitariums in the Boston area. She said to me, "Please don't take out my ovaries because the sanitarium is full of people who had their ovaries taken out."

In 1937, we investigated 10 patients and

studied their FSH determinations and their histories. They were all 40 years of age and had been operated upon 5 years previously. Two separate FSH determinations were done on each patient. Seven patients had a negative FSH determination and no signs of the menopause. We assumed that their ovaries were functioning. Three patients did have signs of the menopause and a positive FSH determination so we concluded that their ovaries at that time were not functioning properly.

About 10 years ago I operated on a patient with carcinoma of the cervical stump in whom supravaginal hysterectomy was done 17 years before. She had not menstruated but she had fresh corpus luteum in one ovary at the time of operation so we considered the ovaries were functioning. I operated upon another woman 10 years after total hysterectomy and she also had fresh corpus luteum in an ovary.

It is my feeling that Dr. TeLinde and Dr. Wharton have done a splendid job in demonstrating that the ovaries function after hysterectomy. My attitude is that much depends on the psychology of the patient. It is wrong to castrate a woman in the age of sex activity, especially if her married life is happy. It is not

good to castrate her even at the age of 50 or 55 if she has evidences of estrin production because she will get an inferiority feeling about her sex life and her husband, with his testicles, has an unconscious superiority feeling. I believe it is very important not to castrate women if their married lives are happy as far as sex is concerned.

DR. S. LEON ISRAEL, Philadelphia, Pennsylvania. The discussants have so far not pointed out one of the important collateral observations of Drs. Telinde and Wharton, namely, that 4 of the 5 animals subjected to unilateral oophorectomy demonstrated hypertrophy and increase in size of the remaining ovary. I think this is an important observation for us to remember because this seemingly occurs in the human ovary. I think we have all had the experience of seeing patients previously subjected to unilateral oophorectomy whose remaining ovary has been threatened with removal because someone has found that it is two or three times the normal size. This is an important observation and ought not to be omitted from this discussion.

DR. WHARTON (Closing). I expected that Dr. Greene would agree with us because of his previous work on the rat. I expected that Dr. Sturgis would not agree because of his Harvard background as contrasted to our Hopkins background. I am glad that we are not too far apart in our agreements as to the effect of hysterectomy on the ovary. In the work it was important to ascertain whether we had a firm foundation to

leave ovaries which appeared normal at the time of operation.

Also as part of the work FSH studies and determinations had to be done. That was important as a part of the study. Unfortunately we did not have proper metabolic cages to get proper urine samples, and monkeys do not cooperate so our samples are subject to error in collection and to contamination. I believe the FSH determinations, unfortunately, are totally inconclusive in this study.

We were aware of Dr. McCall's work and have mentioned his report of ovarian function following radical hysterectomy in our paper as further evidence. There is other evidence of ovarian function in humans following hysterectomy. Bancroft-Livingston has used vaginal cytology in many women and has concluded that there has been no hastening of the menopause as a result of hysterectomy.

The compensatory hypertrophy of the ovary after hysterectomy is an observation which has been made in the past but has been relatively unappreciated. Dr. Israel, I thank you for bringing this point out and emphasizing it. What the mechanism of this is we are not sure, but nevertheless the remaining ovary which does become enlarged, at least in the monkey, is quite normal. It is a hyperplasia of all elements. The follicular apparatus remains intact and there is continuing evidence of follicular development maturation, regression, and corpus luteum formation and regression that one would expect in a normal ovary without hyperplasia.

Autopsy comparison of cardiovascular changes in castrated and normal women

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OVARIAN cancer is unquestionably one of the most lethal forms of malignancy seen by the gynecologist. This type of pelvic tumor is frequently "silent" and completely asymptomatic until adjacent organs are involved, at which time it has already progressed beyond any reasonable hope of salvage. It is a sad but true commentary on this particular form of genital cancer that most cures are in the few women who have an unsuspected adnexal mass noted in the course of routine pelvic examination. The dismal prognosis of ovarian cancer in general is more than verified by the 15 to 20 per cent salvage noted in most reports, although inclusion of various neoplasms of low-grade malignancy may serve to account for a somewhat higher salvage in some series.

It is small wonder that many gynecologists have felt it desirable to remove all ovarian tissue in women requiring any type of pelvic laparotomy if the patient is approaching the menopausal era. It is rationalized that in such women the ovaries are fast approaching senescence; as functionless organs they cannot in any way help the patient but may well serve as a future site for the development of ovarian cancer. Actually, at our own clinic it has been customary for most

of the staff members to practice castration beyond an arbitrary age of 45 years. In the somewhat younger woman unilateral salpingo-oophorectomy has been performed with the thought that one ovary might serve as well as two and that unilateral adnexectomy would decrease the incidence of this disease. We, however, deviate from this rather flexible routine if the patient has any specific desires concerning preservation of the ovaries. Likewise, it has not been the policy to remove adnexa routinely in the course of vaginal hysterectomy regardless of age or accessibility, and it is likely that this somewhat paradoxical situation has been uniform in a good many sections of this country.

There is no doubt that removal of all ovarian tissue will prevent a certain number of women from developing ovarian tumors, some of which may be malignant. In a recent group of 200 cases of ovarian cancer from the files of The Johns Hopkins Hospital, 15 patients had experienced prior pelvic laparotomy. Obviously, these 15 women (almost 8 per cent) would not have developed gonadal cancer had castration been performed at the original operation. It should be added, however, that in 6 women the earlier operation had been performed at so young an age (less than 35) that oophorectomy seemed not only undesirable but unjustified.

In a much larger group of 1,500 patients with ovarian cancer seen from 1930 to 1952, Counsellor and associates⁴ found that 4.5

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Society, Williamsburg, Virginia,
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per cent had had previous hysterectomy. In 80 per cent of these hysterectomized individuals, removal of the uterus had been accomplished 5 or more years before discovery of the ovarian cancer. Although one third of Counsellor's patients who had had hysterectomy were less than 40 years of age at the time of operation, less than 5 per cent of the cases of ovarian cancer occurred in this age group, and Counsellor concludes that castration before age 40 should be rare. A number of authors have commented on the desirability of castration in the 40-year-old woman to obviate the development of ovarian malignancy, but this is by no means a uniform opinion. Hollenbeck,¹² for example, points out that only a small proportion of women who develop ovarian cancer have had prior pelvic laparotomy. He derides any attempt to practice prophylactic oophorectomy, because of the vast number of women precipitated into a menopause in contrast to the rare case of ovarian cancer that might be prevented.

We are, of course, in complete accord with the current gynecological tendency to remove the uterus if both ovaries or tubes are removed. There is little justification for preserving a functionless procreative organ which might well develop tumors, hemorrhagic tendencies, or even cancer, although these sequelae are not common in the castrated woman. While we may conclude that hysterectomy should accompany oophorectomy, the reverse is not true, and Dowsett⁵ has indicated that too many ovaries are being needlessly sacrificed at the time of operation.

We likewise deplore haphazard oophorectomy in the young patient and thereby disagree with Grogan and Duncan,⁹ who contend that a woman's best interests are served by castration at the time of hysterectomy irrespective of age. This judgment is based, not on the fear of later ovarian cancer, but on their opinion that (a) hysterectomy may be followed by such profound degenerative changes as to render the ovaries unfit for sustained physiological function and (b) exogenous hormone therapy is more than

adequate replacement. A more recent article by Grogan⁸ admits that posthysterectomy ovarian function is satisfactory unless the indication for operation had been menometrorrhagia, with associated large painful ovaries, or cystic ovaries as a sequel to previous laparotomy. These comprise some 80 per cent of his cases, and we remain unconvinced.

Exactly the opposite point of view is expressed by Randall and his co-workers¹⁷⁻¹⁹ in several different publications. Although they do not deny that ovarian cancer is a lethal disease and not uncommon, statistics based on communities where cancer is a reportable disease indicate that the probability of its development is only 0.9 per cent until the forty-fifth year, after which the incidence begins to decline. These same authors point out that routine oophorectomy would lead to only a slight reduction of ovarian cancer simply because the vast majority of 40-year-old women have not experienced previous pelvic operation. They further note that, of women who go on to develop ovarian malignancy following laparotomy, a significant proportion are operated on at such an early age (twenties and early thirties) that even the warmest advocates of oophorectomy might be expected to avoid castration. Finally, it is felt that exogenous hormone therapy may be at best an inadequate substitute for removal of the gonads. It is this last contention that is currently arousing considerable speculation among some gynecologists, but it has excited a great deal more interest in the fields of endocrinology and internal medicine.

Griffith⁷ has pointed out the role of the ovary, even in the climacteric woman, as an intricate cog in the delicately balanced endocrine mechanism. While the field of endocrinology still needs clarification, there are few who would deny that some kind of hormonal equilibrium does exist, probably dominated by the pituitary. Griffith specifically mentions a guarding effect of the ovary against the advent of atherosclerosis, and most cardiologists accept a certain therapeutic and prophylactic effect of the estro-

genic hormones in this condition. Masters¹³ states that "although the menopause represents a major involutional phase in ovarian function, it should not be regarded as the end point." Randall has recently utilized vaginal smears to point out in convincing fashion that the postmenopausal vaginal mucosa often shows active evidence of estrogen stimulation for as long as 15 years after the cessation of menses. The correlation of cornified vaginal mucosa and circulating estrogen seems well established.

Of particular importance is a study by Wuest and associates²² which indicated that a group of 49 surgically castrated women develop arteriosclerosis more extensively and earlier than control patients. They state that oophorectomized patients at the age of 50 develop a degree of atherosclerosis comparable to that in a control group of 70 years. Although the mechanism is still uncertain, it would appear that castration is followed by a rise in certain blood lipids (not necessarily cholesterol), which may induce or hasten the formation of abnormal vascular degeneration. A more recent publication by Robinson and co-workers²⁰ deals with a group of oophorectomized women in whom there was a significant reduction in elevated serum lipids after estrogen therapy. They conclude that estrogen represents a logical therapeutic approach to coronary heart disease in such women, and certainly many internists treat arteriosclerotic male patients with estrogenic substances despite the often distressing feminizing side effects.

In the uncertainty regarding the desirability of routine oophorectomy during the course of operation for benign disease one consideration seems inescapable. If it can be proved that castration is followed by a disproportionately high incidence of arteriosclerosis or other metabolic disorders, it might be preferable to conserve all possible ovarian tissue regardless of age. Admittedly, the occasional case of ovarian cancer developing in such postlaparotomy patients will prove distressing; yet a much higher incidence of such conditions as angina pectoris, paroxysmal nocturnal dyspnea, or hyper-

tensive encephalopathy hardly offers a preferable alternative.

Material

It was with such thoughts as these that we decided to carry out a study comparing the cardiovascular changes in castrated and noncastrated individuals. The basis for our study is 85 patients who subsequently came to autopsy at varying intervals after bilateral oophorectomy. If there was any question about estrogen therapy or doubt that all ovarian tissue had been removed, the case was discarded.

Cardiovascular changes were compared with those in 250 similar control patients from autopsy files. The cause of death in both groups seemed essentially comparable as was the age at death. To the best of our knowledge both control and castrated patients were drawn from completely similar and unselected groups and would thus seem statistically comparable to one another. Obviously, however, autopsy findings and statistics may not be equated with similar groups of live patients. This approach appeared to offer a more accurate and precise anatomical basis than study of live patients (Table I).

There have been several recent publications by Robinson and associates²¹ and Oliver and Boyd¹⁶ which suggest that castrated women have a much higher incidence of coronary artery disease than control patients. Their conclusions are based primarily on such subjective signs of coronary insufficiency as chest tightness (angina pectoris) with or without electrocardiograms, which are often misleading. We submit that such data are not as objective and precise as that obtained at autopsy.

In addition, simple obesity observed in castrated women by Oliver and Boyd (35 pounds as compared to 9 pounds in control patients over a 10 year span) could be expected to induce more dyspnea and chest discomfort as well as perhaps more cardiovascular disturbance. Finally, such clinical observations as ophthalmological study of the eye grounds, blood chemistry and pres-

Table I

<i>Method of study</i>		
85 castrated	} patients	{ 1. Similar decades; uniform causes of death 2. No known history of estrogen therapy 3. Where castration, complete ablation of all ovarian tissue
250 control		
<i>Criteria for arteriosclerosis</i>		
1. Aorta	}	Marked arteriosclerosis only as noted by a number of pathologists. All data statistically valid but comparable only to autopsy (not live) patients.
2. Coronary artery		
3. Cerebral artery		
4. Peripheral artery		
<i>Not included</i>		
Heart weight; blood pressure or lipids; osteoporosis		

sure, and electrocardiography, while helpful, are not infrequently normal though coexistent with severe cardiovascular disease.

Like Wuest, we attempted to utilize two main types of data as found in postmortem studies. The weight of the heart with comparative measurements of the ventricles was noted, but marked variation due to such obvious factors as weight, state of nutrition, and body type made this of negligible value. Blood pressure recordings, frequently on very ill patients admitted in extremes via the accident room, were not felt to be valid and were not included in this study.

Much more reliable was the degree of arteriosclerosis as manifested especially by the coronary vessels and aorta, although we are cognizant that atheromatous changes in the aorta and coronary vessels do not always parallel one another in some strains of animals. Indeed, certain Oriental races with a low incidence of coronary artery disease have extensive atherosclerosis of the aorta as noted at autopsy, and this inconsistency has been found in cholesterol-fed cockerels by Hojman and associates.¹¹

Unlike Wuest, we did not rely on exact measurements in simply calibrating the lumen of the coronary vessels, but depended instead on the recorded observations of the pathologist in regard to both coronary and aortic vessels. While we may be criticized for a certain lack of the exactness manifested by Wuest, it was not difficult to separate cases into those showing marked, moderate, or minimal changes. Indeed, a very recent publication by Hirst and co-workers¹⁰ has indicated the accuracy of gross inspection in the evaluation of postmortem atheromatous changes. Autopsy studies were performed by various senior pathologists of our Pathology Department.

The number of pathologists reviewing the cases would seem also to militate against any personal ingrained idiosyncrasies. We ourselves did not personally review each case, preferring the unbiased opinion of the pathologists long before we contemplated this type of review. Available to us were gross and histological descriptions of the organs as well as hematoxylin and eosin-stained sections with frequent corroborative

Table II. Autopsy findings (ratio per decade of patients with marked arteriosclerosis to the total number of patients)

<i>Age of patient</i>	<i>Ratio among castrated patients</i>	<i>Ratio among control patients</i>
Below 30	0/3—0%	2/39—5%
30-40	1/9—11%	8/40—20%
41-50	3/15—20%	9/47—19%
51-60	13/32—41%	14/41—34%
61-70	14/20—70%	31/42—74%
Above 70	4/6—67%	25/41—61%

elastic connective tissue and fat stains. From this composite we are convinced of an ability to obtain a valid impression of the cardiovascular system in the cases reviewed. The results may be tabulated as shown in Table II.

Table II includes both postsurgical and control groups of patients listed in the respective decades of death. It is obvious that certain decades are represented by a mere scattering of patients which might lead to inaccuracy. As it stands, however, there is little apparent statistical deviation between the two groups, and the only significance lies in the close similarity. The total deviation between the two groups as noted, 41 and 36 per cent (Table III), for castrated and control women, respectively, is so slight as to be regarded as approximately equivalent. While we ourselves make no pretense to be statisticians or mathematicians, we have been assured by our Biostatics Department that the slight deviations noted are well within statistical laws of chance.¹⁵

Table IV shows the time interval between operation and autopsy, divided into 5 year spans, and the number and percentage of patients showing marked arteriosclerosis are tabulated along with the mean age and interval between operation and death. While it might appear that there is a disproportionate rise in the incidence of arteriosclerosis in those women dying more than 5 years after operation, comparison of their mean age at death with that of control patients fails to show any relevant statistical derivation.

Table V concerns the patient's age at the time of castration. We wondered if oophorectomy in the younger patients with functionally active gonads might be more influential in instigating the changes leading to arteriosclerosis. Thus, 10 years after operation was arbitrarily selected as an adequate minimum for changes to develop, and we have grouped patients in decades according to the initial age at operation. Although 10 years is the minimum interval since operation, many patients were followed much longer than that, up to 53 years, before death. Twenty-

four postcastration patients died within 10 years of operation; the remaining 61 deaths are shown in Table V.

Table V shows practically no cardiovascular difference as regards age at the time of castration followed by a minimum 10 year survival. This 10 year figure was picked arbitrarily as allowing sufficient time for development of cardiovascular changes yet also permitting the follow-up of a sufficient number of patients. Actually, most women lived more than one decade, and some lived as long as 53 years after operation.

Comment

During the initial preparation of this material we had anticipated finding an increased incidence of degenerative cardiovas-

Table III. Total number of patients with arteriosclerosis, castrated and control

	<i>Marked arterio- sclerosis</i>	<i>Total patients</i>	<i>% with arterio- sclerosis</i>
Castrated	35	85	41
Control	89	256	36

cular changes in the castrated woman. Therefore, our findings were, to say the least, surprising to us, but should indicate our own complete lack of prejudice in evaluating cases. It should be pointed out that certain groups in the tables comprise only a relatively few cases. These should not be interpreted too precisely, but our totals seem much more statistically impressive. Above all, we emphasize that our figures are simply published as they occurred.

We can offer no ready explanation for our divergence from previous publications. While this study embraces a longer series of cases than most comparable ones, it should be apparent that in some groups there are insufficient patients to unequivocally exclude sampling error and chance.

At this writing, the exact status of increased blood lipids and their relationship to atherosclerosis is highly uncertain. Eder,⁶

Table IV. Incidence of arteriosclerosis in relation to time interval between castration and death

Years postoperative at autopsy	Mean age		No. patients	Marked arteriosclerosis		Control incidence of arteriosclerosis (%)
	At operation	At death		No.	%	
2-4	44	46	14	2	14	19
5-10	44	53	14	5	35	34
10-15	38	50	19	8	42	34
15-20	40	59	11	4	36	34
20-25	36	56	10	4	40	34
More than 25	31	64	17	9	53	74
All patients	38	54	85	33	38.9	34

for example, has stressed a need for clarification of the respective importance of the serum lipids and the lipoproteins, and all of us are aware of the controversy in regard to cholesterol ingestion. At the same time, it must be understood that, even if oophorectomy should produce estrogen depletion and elevated blood lipids, a hastened or extreme degree of cardiovascular degeneration is not inevitable. Our medical confreres are agreed on this although still uncertain as to the exact relationships between estrogens, blood lipids, and atherosclerosis. Indeed, Altschule¹ has pointed out that stilbestrol can actually induce atherosclerosis in certain chicks, although the blood level of cholesterol, beta-lipoproteins, and total polysaccharides are not elevated.

Whether the castrated woman represents a real entity in regard to cardiovascular disease may be regarded as uncertain, but we have found nothing to substantiate the belief. Although it is difficult to deny the guarding effect of estrogen against atherosclerosis, we must ask if oophorectomy always causes an abrupt drop in circulating estrogens, for the ability of the adrenal to supplement ovarian production is well established. McBride¹⁴ has noted that the estrogen blood level of surgically castrated women is only slightly lower than that found normally in the postmenstrual phase of the cycle.

More astonishingly, Bulbrook^{2, 3} has reported significant levels of urinary estrogen in women with breast cancer who have had extirpation of ovaries, adrenals, and hypoph-

ysis. It would seem that ablation of the ovaries, as well as other endocrine organs, does not necessarily indicate invariable depletion of estrogen. Perhaps other sources exist; conceivably supplements of this steroid may be found in the diet from many sources, some of which have been highly publicized in the lay press recently. Indeed, the much discussed and highly incriminated cholesterol is closely related chemically to the estrogenic substance and might easily be converted into such a steroid.

In any case, our results indicate that castration itself does not necessarily initiate a chain of events culminating in frequent degenerative disease. With this thought in mind we shall continue our present policy of conservatism in the young with routine oophorectomy reserved for the postmenopausal patients and always influenced by the appearance of the gonad. Irrespective of age, however, we shall not feel we are inducing a cardiovascular catastrophe by performing oophorectomy at any age if it appears to be surgically indicated.

Table V. Age at castration with autopsy 10 years (or more) later

Age at operation	No. of patients*	No. with arteriosclerosis	% with arteriosclerosis
Below 30	14	6	43
30-40	25	9	36
41-50	18	6	33
51-60	4	2	50

*Twenty-four patients died less than 10 years postoperatively; some patients lived up to 53 years postoperatively.

Conclusions

1. Oophorectomy, in conjunction with hysterectomy for benign disease, has usually been considered preferable in immediately pre-menopausal women because of the desirability of removing gonads that might later develop cancer. More recent investigation has suggested that such castration might be followed by an inordinately high incidence of arteriosclerosis. This current study has attempted to compare surgically castrated (85) and control (250) patients whose cardiovascular systems were studied at various decades of death and at various intervals

postoperatively. This is a preliminary study based on autopsy cases.

2. Although this series of castrated and control patients is statistically comparable, no significant differences in the incidence of arteriosclerosis could be noted regardless of initial age at operation or years intervening before death.

3. Henceforth, our clinical concept is to perform oophorectomy where indicated, without taking into consideration inevitable cardiovascular changes and without feeling that replacement therapy is necessary unless subjective symptoms demand it.

REFERENCES

1. Altschule, M. D.: *M. Sc.* 127, 1960.
2. Bulbrook, R. D., and Greenwood, F. C.: *Brit. M. J.* 1: 666, 1957.
3. Bulbrook, R. D., and Greenwood, F. C.: *Brit. M. J.* 1: 662, 1957.
4. Counsellor, V. S., Hunt, W., and Haigler, F. H., Jr.: *AM. J. OBST. & GYNEC.* 69: 538, 1955.
5. Dowsett, J.: *West. J. Surg.* 63: 156, 1955.
6. Eder, H. A.: *The Effect of Sex Hormones on Serum Lipids and Lipoproteins. Hormones and Atherosclerosis*, New York, 1959, Academic Press, Inc.
7. Griffith, G. C.: *Obst. & Gynec.* 7: 479, 1956.
8. Grogan, R. H.: *Obst. & Gynec.* 12: 329, 1958.
9. Grogan, R. H., and Duncan, C. J.: *AM. J. OBST. & GYNEC.* 70: 1277, 1955.
10. Hirst, A. E., Jr., Gore, I., Hadley, G. G., and Gault, E. W.: *A. M. A. Arch. Path.* 69: 110, 1960.
11. Hojman, D., Pellegrino-Iraldi, A. A., Malinow, M. R., Pick, R., Stamler, J., and Katz, L. N.: *A. M. A. Arch. Path.* 68: 533, 1959.
12. Hollenbeck, Z. J. R.: *Ann. Surg.* 21: 442, 1955.
13. Masters, W. H.: *AM. J. OBST. & GYNEC.* 74: 733, 1957.
14. McBride, J. M.: *J. Clin. Endocrinol.* 17: 1440, 1957.
15. Merrill, M.: Personal communication.
16. Oliver, M. F., and Boyd, G. S.: *Lancet* 2: 690, 1960.
17. Randall, C. L.: Personal communication.
18. Randall, C. L.: *AM. J. OBST. & GYNEC.* 73: 1000, 1957.
19. Randall, C. L., and Harkins, J. L.: *AM. J. OBST. & GYNEC.* 74: 719, 1957.
20. Robinson, R. W., Higano, N., and Cohen, W. D.: *A. M. A. Arch. Int. Med.* 100: 739, 1957.
21. Robinson, R. W., Higano, N., and Cohen, W. D.: *A. M. A. Arch. Int. Med.* 104: 908, 1959.
22. Wuest, J. H., Dry, T. J., and Edwards, J. E.: *Circulation* 7: 801, 1933.

Discussion

DR. CLYDE L. RANDALL, Buffalo, New York. Certainly we would like to know if and how often castration results in metabolic changes which increase the rate of vascular aging and hasten arteriosclerosis and the earlier death not unlikely with cardiovascular disease. Few will question the pathologist's autopsy record as a reasonable estimate of vascular change. Although I admire the objective manner in which this study was conducted and the findings reported, I do not altogether agree with the authors' conclusions, for reasons to be mentioned.

First, the percentage of controls showing arteriosclerosis at autopsy is high in comparison with the data reported by others. From the Mayo Clinic consistently lower figures have been reported, based on the autopsy findings of 100 women dying in each decade.

Among noncastrated women coming to autopsy in their 40's, the authors noted that 19 per cent had marked arteriosclerosis. Ackerman, Dry, and Edwards' figure was 14 per cent. At Hopkins marked arteriosclerosis was found in 34 per cent of women dying in their 50's; the

Mayo Clinic figure was 22 per cent for the same age group. Novak and Williams suggest that 74 per cent be regarded as an expected incidence of marked arteriosclerotic disease among women in their 60's, but Ackerman, Dry, and Edwards found a supposedly equal degree of arteriosclerotic disease in only 36 per cent of the women dying within this same decade. Perhaps the individuals regarded as controls by Novak and Williams should not be regarded as a conclusive picture of what is normal or usual for the noncastrated women.

In the authors' Table IV, 10 to 15 years after castration at a mean age of 38 years, there were 19 women who came to autopsy at a mean age of 50 years. Forty-two per cent of these 19 castrated women had developed marked arteriosclerosis by the time they died at 50 years of age. Thirty-four per cent is the figure given here as the incidence of arteriosclerosis that, according to the authors' Table II, could be expected among women of this age group.

In Table II, however, among the 47 noncastrated women coming to autopsy between the ages of 40 and 50, the incidence of arteriosclerosis was not 34 per cent but only 19 per cent! Why compare the incidence of marked arteriosclerosis observed among castrated women dead by a mean age of 50 years with the incidence of vascular changes among noncastrated controls who came to autopsy in the decade 50 to 60?

I am sure I would be less inclined to question their interpretation of their data if the authors had estimated the degree of estrogenic effect or the deficiency of estrogenic effect in the tissues of the castrated patients and in the control patients. In data presented to this Society 3 years ago, we pointed out that, at least as evidenced by vaginal smears, 10 to 15 years after castration the tissues of nearly 50 per cent of women indicate a compensatory extraovarian source of estrogen after castration.

Looking at data in Table V, we see that, 10 or more years after castration, of 14 women castrated before the age of 30, 6 or 43 per cent had developed marked arteriosclerosis. Among 25 others castrated between 30 and 40 years of age, 9 or 36 per cent had developed marked arteriosclerosis.

Considering, however, the probability that 10 years after castration only 50 per cent of the castrated women can be expected to show moderate to marked deficiency of estrogenic effect,

does this not suggest that, of the 14 women castrated before the age of 30, only 7 were presumably not protected against the estrogen-depriving possibility of castration by extrapelvic sources of estrogen? Does it not appear quite striking that of the 7 who could be expected to show effects of estrogen deficiency, 6 or 85 per cent did indeed show a marked degree of arteriosclerotic disease at autopsy? In the same Table V, of 25 women castrated in their 30's, realizing that 12 of this group would probably be protected by extrapelvic sources of estrogen against the effects of the estrogen-depriving possibilities of castration, is it not significant that of the 12 or 13 women who *could be* expected to have experienced estrogen deficiency after castration, 9 (72 per cent) did indeed come to autopsy showing a marked degree of arteriosclerotic disease.

These are all interesting data, of course, but let us not forget that factors other than estrogens in the circulating blood may help protect the younger menstruating woman from arteriosclerosis. Recent reports by Astrup and others suggest that during menstruation fibrinolytic principles absorbed from the intrauterine pool of menstrual debris and the venules of the breaking down endometrium may result in a monthly lytic destruction of any fibrinous depositions within the small vessels of the woman whose metabolism and diet may be predisposing her to arteriosclerosis. If such monthly lysing effect does occur the first fibrinous steps toward the formation of atheromatous disease, throughout the years when menstruation recurs regularly, should fail to reach the progressive stages which eventually we recognize as arteriosclerosis. Certainly, the data presented by Novak and Williams suggest that we should no longer belabor the importance of ovarian preservation as a means of protecting women from the possibility of premature vascular aging to the neglect of the other factors probably involved.

Let me emphasize again that I do not doubt the accuracy nor the significance of the authors' observations. I do object, however, to assuming that such observations will permit us to conclude that depriving any individual woman of her ovaries—perhaps her only source of estrogenic effect—is not likely to increase the risk of serious arteriosclerotic disease in the future for that individual. Perhaps I am really objecting only to an effect of maintaining so objective and unbiased a point of view when we are looking

for evidence of relationships which we suspect. As regards the authors' data, my own obviously biased conclusion would be that we should not permit the averaging effects of what happens to a large number of castrated women to obscure our view of the fate of admittedly only that proportion of women whose inability to protect themselves with estrogen from extraovarian sources provides us but a few who can illustrate the really undesirable effects of castration. These few are the individuals to watch if we are looking for evidences of the undesirable effects of castration. Let us, therefore, not lose sight of what happens to them, no matter how impressed we may be by the design of a kind Providence which enables approximately one half, at least of American women, to tolerate even castration with outward calm and unruffled intimae.

DR. C. LEE BUXTON, New Haven, Connecticut. Drs. Novak and Williams have focused their attention on one important aspect of the effects of castration in the female. Three years ago at a meeting of this Society Dr. Randall, the previous discussant, stated "it is difficult to ignore evidence that estrogen protects women from arteriosclerosis." Novak and Williams are presenting evidence that the castrated woman may be involved in arteriosclerotic changes no more frequently than the normally menopausal woman of the same age.

Although I find it a little unnatural to be in the position of being an advocate of retaining the ovary, it must be said that there are several aspects of the cases in the authors' series that need a little further clarification before the conclusions could be considered entirely tenable.

There has been no thesis on the part of either the protagonist or antagonist of ovarian conservation that castration per se is the essential factor in the development of vascular changes and other symptoms following ovarian removal. The question rather is whether or not the absence of estrogen, which presumably occurs following castration, is the cause of these physical abnormalities. Therefore, it would be most important not only in Novak and Williams' cases but in any other cases presented, as Dr. Randall just stated, to know whether or not there was any unexpected endogenous or known exogenous source of estrogen which might nullify the estrogen depletion effect of ovarian removal.

Almost everyone interested in this subject has commented at one time or another on the sur-

prising variation of evident estrogenic activity in different postmenopausal and postcastrate women. Therefore, it would be important to know, in Novak and Williams' cases, whether any of their castrated autopsy patients had, during their post-castration lifetime, any history of continuous or intermittent estrogen replacement therapy; or if, at the time of autopsy, vaginal epithelium had shown indication of continuing estrogenic activity. These would be difficult if not impossible facts to obtain retrospectively, but were it possible to obtain them it would have been intriguing to compare the incidence of residual estrogenic activity with the development or lack of development of cardiac and aortic arteriosclerotic changes.

Thinking that it might be possible to shed a little more light on this subject by consulting our own autopsy files, I enlisted the interest of a resident in our Pathology Department who reviewed the protocols of autopsies on a number of castrated women. As might be expected, there was nothing in the past history in the autopsy protocol which commented on the administration of exogenous estrogen and, furthermore, microscopic inspection of vaginal epithelium did not happen to be part of the routine of autopsy technique of our Pathology Department. Our attempts at further illumination of the subject, therefore, came to an abrupt halt.

As I see it, there are only two reasons for salvaging the residual ovary in a woman being operated upon when she has passed the child-bearing age. The first is that there may be some product, presumably hormonal, besides estrogen in the ovary which is as yet unknown and of which the woman is being deprived. It is hard for me to believe that estrogen deprivation in itself should be a serious factor. Contrary to what Griffith says, I believe that we, as endocrine gynecologists, find estrogen replacement cheap, easy, and efficient and a small price to pay for possible future dangers or operative inconveniences which might arise from the residual ovary. The second reason, commented upon everywhere, is the very definite psychologic implication to the patient concerning complete ovarian removal, and this is certainly a most important factor.

These to me are the two questions which must be faced when this problem presents itself. The answer to these two questions versus potential dangers, whatever they may be, to ovarian preservation must be weighed in the balance and action taken accordingly.

DR. NOVAK (Closing). Our results were just as big a surprise to us as they were to Dr. Randall. We went into this study more or less expecting to confirm Dr. Randall's work, namely, that the castrated group of individuals has a higher incidence of vascular disturbance. We are simply presenting our material as it occurred and I hope I have impressed upon you that we have merely compiled previously assayed material. The extent of arteriosclerosis was estimated not by one but by a host of different pathologists who had no bias and who only reported matters as they saw them at autopsy.

Dr. Randall has rightly pointed out certain differences in the figures noted at our own and at the Mayo Clinic. I think that this is understandable if you think of the probable differences in the type of patient that you might expect at the two respective institutions. For example, our patients included many Negro women, and I am told that these have a higher

incidence of arteriosclerosis than does the average white patient, although the Bantu African of pure stock has a lower incidence in his natural habitat. I would doubt that the Mayo group was similar, so it is not proper directly to compare these groups. Nor is it statistically valid to compare such patients at autopsy to any group of live women.

In regard to Dr. Buxton's discussion, we are in complete agreement that it is not castration per se that is the causative factor. It is more likely the absence of estrogen. There are probably a great many extraovarian sources of this steroid. My Table I shows that we did not include any patient in whom there was any known history of estrogen therapy, although we cannot deny that this may not have been utilized by outside physicians unknown to us. Finally, like Dr. Buxton, we were unable to include any histologic material from the vagina because our pathologists do not routinely section this organ.

Polycystic ovarian disease

A clinical and experimental study

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DURING the 25 years since Stein and Leventhal first reported the syndrome which bears their names, there have been many hypotheses offered to explain its origin. Although the precise mechanism of production has remained an enigma, research activity in this area has yielded several significant findings.

Closer scrutiny of patients with oligomenorrhea or amenorrhea and infertility disclosed the following:

1. Some cases have distinct differences that make it seem inconsistent to lump them all together in one category labeled the Stein-Leventhal syndrome.¹

2. At least some of the presumably characteristic cystic ovarian changes may be absent or, when present, may be related to an entirely separate entity, e.g., hyperfunction of the adrenal cortex.

3. A few have excessive uterine bleeding prior to the development of oligomenorrhea or amenorrhea which suggests that there is a common factor in patients presenting the two extremes—hypermenorrhea and amen-

orrhea. This further suggests that the Stein-Leventhal syndrome may be only an advanced phase of anovulatory ovarian behavior.

4. The syndrome may have a carcinogenic potential as indicated by the associated development of carcinoma of the endometrium in some instances.²⁻⁴

In a previous report it was noted that relatively normal levels of estrogen and gonadotropin were essential for a favorable response to ovarian wedge resections.¹ We believe these endocrine assays are important diagnostic procedures in selecting patients for operation and in eliminating those patients with similar menstrual abnormalities secondary to decreased amounts of pituitary gonadotropin or primary ovarian failure. This report deals with additional endocrine evaluation of such patients and further clinical application of this premise. Also, in an effort to add to the understanding of the cause or causes of this syndrome, various means of producing similar changes in experimental animals are reported.

Clinical observations

Since 1950 a total of 40 cases which, we believe, properly fit into the category of polycystic ovarian disease have been observed at The University of Michigan Medical Center. All of these patients had in common oligomenorrhea or amenorrhea, infertility, and infrequent or absent ovulation. In addition, all had relatively normal excretory rates of estrogen and gonadotropin (Tables

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Table I. Preoperative endocrine assays

Patient No.	FSH (M.U./24 hr.)	Estrogen (R.U./24 hr.)	17-Ketosteroids (mg./24 hr.)
1	Neg., neg.*	10, 10, 8, 8, 5, 10, 10	9.9, 7.4, 10, 8, 11.8, 4.6, 9.5
2	Neg., neg., * neg., neg.	10, 7, 10, 10	9.6, 8.0
3	Neg., neg., neg., * neg., neg.	10, 10, 20	25, 13.2
4	24, 6, 48, 48	20, 10, 10, <4, 4	9.7
5	6, 6, 6, 6	10, 4, 10, 8	
6	6, 6, 24, 12, 24	10, 5, 10, 5, 10	
7	Neg., 6, 6, 13, 6	10, 8, 10, 5, 4	3.5, 16.7
8	6, 6, 24, 24, 24, 6	10, 5, 20, 20, 20, 4, 5	10.7
9	6, 12, <6, 24, 6	10, 10, <4, 10, 5, 5	19.4, 14.2
10	6, 6	20, <4, 4, 10, 20, 10	14.0, 16.7, 10.7, 7.3, 7.7, 8.6, 8.2
11	6, 6, 6	10, 4, 10	
12	6, <6, 6, <6	5, 8, 10	
13	6, <6, 12, 24	10, 10, 10, 15	
14	6, 12, 12, 12, <6	8, 10, <4, 10	
15	6, 6, 24, 6, 6	10, 5, 10, 8, 5, 10	
16	6, 6, 6	10, 10, 10, 10	14.0
17	<6, 24, 24	10, 10, 10	
18	12, <6, <6, 24, 6	10, 10, 10, 10, 16	13.0, 13.5
19	6, <6, <6, 24	10, 10, 8, 20	
20	3, 3, 3, 6, 12	10, 10, 10, 8, <4	12.9, 14.6
21	3, 3, 6, 6, 12, 6, <6, 6, 6	8, 10, <4, 5, 5, 10, 20, 8, 10, 20, 10, 20, 6, 8	10.7, 16.1
22	<6, 24, 24, 12	20, 8, 10, 5	10.7
23	12, 6, 24, 24, 12, 24	8, 8, 8, 20, 10, 2	9.3, 13.1
24	6, 6, <6, 6	10, 10, 10, 20	19.3, 15.4
25	Neg., <6, 12, <6, 12, <3	5, 10, 20, 20, 20, 20	6.0, 8.5
26	<6, 6, 12, 6	20, 20, 8, 8	11.7
27	48, 6, 3, <3, 12, 6	5, 6, 10, 10, 6, 10	2.8, 5.4

*Negative tests indicating less than 40 M.U. per liter of urine.

I and II). Because there was no therapeutic response to wedge resections in patients with very low or undetectable levels of estrogen and/or gonadotropin, this group was excluded from this study.

Age distribution was that which would be anticipated in a group primarily concerned with infertility. The youngest was 17 and the oldest 40 years of age. Of the remainder, 33 were in the third and 5 in the fourth decade of life.

Histories of these patients revealed marked variation in the menstrual pattern. All except 6 were nulligravidas. Only 3 had had successful pregnancies previously. Fifteen had a delay of the menarche beyond age 13 years, and 3 others had never had a spontaneous menstrual period. Fifteen had not menstruated for more than a year before

operation, and the remainder presented variable degrees of oligomenorrhea. Ten previously had severe hypermenorrhea for which 4 required uterine curettage. In the majority, general physical appearance was normal. Eight were obese. Eighteen had hirsutism and 4 required frequent shaving or depilatory applications. Four were both obese and hirsute. There was no other evidence of masculinization. In most of these, operation seemed only to arrest progression of the hirsutism; but, in 3, there was definite regression.

Repeated attempts to demonstrate ovulation by use of the basal body temperature and serial daily vaginal smears were unsuccessful except in 3 cases. At the end of 14 months of continuous observation, one patient ovulated only once. The presence of a

fresh corpus luteum suggested that another patient had ovulated a few days prior to operation. The fact that some ovulated, albeit infrequently, was evident from the corpora lutea or corpora albicantia sometimes found in the wedges removed from these ovaries.

Variations in the histories of these patients suggest multiple causative factors. Perhaps any situation producing recurrent anovulatory cycles, if unchecked, may induce the ovarian changes characterizing this syndrome. Eleven had basal metabolic rates below -10 per cent. Two were sisters with almost identical findings and therapeutic results. Four developed their menstrual abnormality immediately after a pregnancy.

Endocrine assays

Serial determinations of excretory rates for estrogen and gonadotropin were carried out in all patients (Tables I and II). In some, the period of endocrine investigation extended into the postoperative period. For at least a month preoperatively and postoperatively, several patients were subjected to intensive endocrine survey, including not only serial estrogen and gonadotropin determinations but also urinary excretory levels of 17-ketosteroids, luteinizing hormone, pregnanediol, and pregnanetriol.

During the early years of this study, a qualitative procedure was used for the evaluation of urinary gonadotropin. This test was based on the response of the immature

Table II. Preoperative endocrine assays

Patient No.	FSH (M.U./24 hr.)	Estrogen (gammas/24 hr.)	17-Ketosteroids (mg./24 hr.)	Pregnanediol (mg./24 hr.)	Pregnanetriol (mg./24 hr.)
28	<6, 12, 48, 12, <24	5.1, 5.0	18.3		
29	<6, <6, <6, 3, <6, 12, 12, 12, 6, 12, 12, 12	8, 2, 10, 8, <4, 3.6, 2.2, 5.6, 2.1, 4.5, 5.0, 5.6	12.8, 16.9, 14.8	1.34, 1.317, 0.566, 1.163, 0.95, 1.25, 1.62	0.329, 0.213
30	<6, 12, <6, <6, 12	2.9, 13.8, 7.6, 4.7, 6.0, 5.7	6.7, 3.6	1.13, 1.44, 0.70, 1.63, 2.37	0.48
31	<6, 6, 12, 6, 6, 6, 6, <6, 12, 12, 12, 12, 12, 12	6, 2, 2, 2, 40, 6.0, 4.5, 1.6, 3.0, 5.6, 3.4, 2.5, 4.5, 4.5, 3.0	5.7, 9.9, 4.9, 9.7, 6.1	1.31, 2.17, 1.43, 0.80, 1.327, 0.773, 1.29, 1.5, 1.413, 1.413, 1.36, 1.785, 1.73, 1.92	1.320, 0.626
32	12, 12, 12, 24, 48	6.4, 3.6, 2.6, 4.0, 5.6	14.2, 11.1, 9.16	0.553, 4.83	<.01, 1.098
33	24, <6, 12, 12, 6, <6, 12, <6, 12, 12, 12, 12, 12, 12	6.9, 11.7, 4.4, 9.0, 3.3, 4.0, 3.5, 4.0, 2.7, 4.0, 2.6, 3.4, 6.3	20.9, 13.8, 16.6, 4.2, 8.8, 12.3, 12.1, 14.3	1.65, 0.904	1.80, 0.765
34	<6, 12, 24, 24, 24, 24, 24, 24, 24, 24, <6	5.0, 7.2, 6.3, 4.5	10.9		
35	<6, 6, 6, 12	3.4, 2.4, 1.7, 2.9	7.3, 11.5, 10.2, 10.0, 11.3, 4.1, 12.25, 13.5	0.43, 1.35	0.200
36	12, 24, 12, <6, 12, 12, 24, 6				
37	12, <6, 6, <6, <6, 6, 6	7.8, 16.8, 14.0, 5.6, 8.2, 6.0, 8.8, 8.4, 11.6, 5.5, 5.7, 3.6, 1.2, 1.8	15.4, 9.4, 15.5	1.045, 1.125, 1.00, 0.38, 1.105, 1.845	0.66, 0.47
38	6, 6, 3, 3	6, 10, 10, 10	17.2, 21.2, 11.4		
39	12, 12, <6, 6, 12, 24, 12, 12, 6, 24, 12, 12, 12	6 R.U., 5.7, 6; 6.6, 2.3, 5.5, 2.9, 4.3, 11.8, 6.3, 2.3	10.3, 7.6	1.6, 2.34, 1.73, 1.72, 1.05, 1.61, 1.83, 1.62, 0.77	0.65
40	12, 12, 48, 12	4.4, 22.6, 8, 4.0	12.7, 4.4, 19.2, 8.4	0.98, 1.36, 1.5	0.01, 0.01



Fig. 1. Ovary of a patient with polycystic ovarian disease following removal of the wedge of tissue.

mouse uterus to an alcohol precipitate of 25 ml. of urine from a first morning specimen. A negative test indicated the absence of primary ovarian failure. Later, this method was supplanted by the procedure of Klinefelter, Albright, and Griswold⁵ which per-

mits estimation of the rate of excretion of gonadotropin. The alcohol precipitation method for recovering gonadotropin was later replaced by the kaolin-acetone method.⁶ Recently, the assay procedure has been refined and rates of gonadotropin excretion

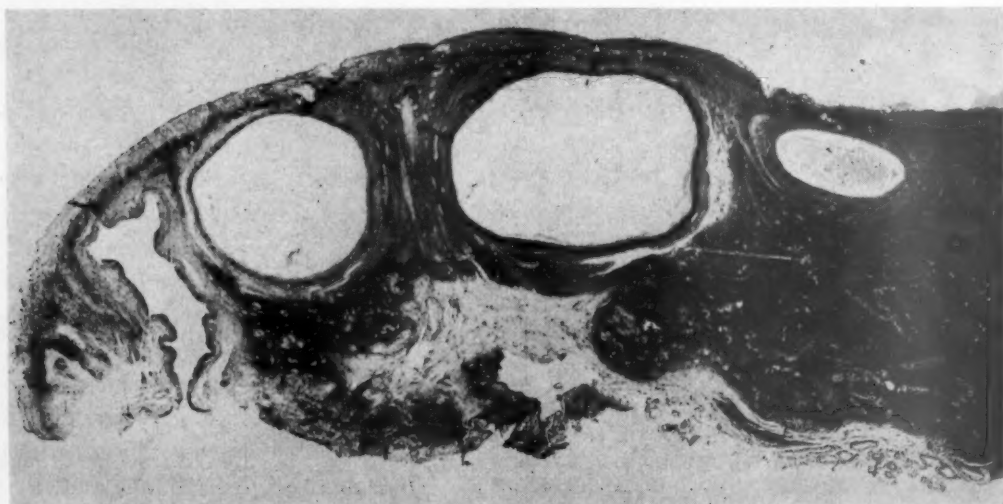


Fig. 2. Section of ovary from Patient J. L. (Fig. 5). Note markedly hyperplastic follicle with irregular contours at extreme left. ($\times 8$.)

are expressed in terms of a laboratory standard human pituitary gonadotropin extract, HMG (P).*

The prostate response of immature, hypophysectomized male rats was used as a test for luteinizing hormone.⁷ The gonadotropin extract from a 2 or 4 hour aliquot of a 24 hour urine specimen was used for these tests. Three animals were used for each determination and the mean prostate weights recorded as an index of LH excretion.

Urinary estrogen was recovered by a modification of the method of Gallagher and associates.⁸ The extracted estrogen was dissolved in convenient amounts of propylene glycol and estrogenic activity measured by the Allen-Doisy method,⁹ or, more recently, by the mouse uterine method.¹⁰ In the latter method, the rate of excretion is expressed in terms of estrone equivalents.

Excretion rates for 17-ketosteroids were determined by the method of Robbie and Gibson.¹¹ The Eberlein-Bongiovanni¹² paper chromatography method was used for pregnanediol determinations, and a modification of this method was employed for pregnanetriol measurements.

Operation

Following the preliminary endocrine investigation, all patients were subjected to bilateral ovarian wedge resections. Between one third and two thirds of each ovary was removed following elliptical incisions along the longitudinal axis (Fig. 1). Fine chromic catgut was used to close the ovarian defect.

At the time of laparotomy, the ovaries of all but one were grossly typical of changes ascribed to the Stein-Leventhal syndrome—pale gray in color, relatively smooth with thickened capsules and multiple small cysts packed beneath the tunica. In 11, the ovaries were not enlarged; in 26, they were slightly enlarged (4 cm. or less); and, in 3, the ova-

ries measured between 4 and 6 cm. Although one patient had grossly normal ovaries, the characteristic microscopic follicular hyperplasia was present without appreciable cyst formation. Another patient (not included in this group) with ovaries typical of polycystic ovarian disease proved to be in an entirely different category with hyperfunction of the adrenal cortex. These exceptions indicate the hazard of relying for diagnosis only on the gross appearance of the ovaries.

In all of these patients, there were varying degrees of follicular hyperplasia usually involving both granulosa and theca interna layers (Figs. 2, 3, and 4). There was marked variation in the amount of cyst formation, as well as in the appearance of lining granulosa cells. Evidence of luteinization was usually absent. In a few, corpora albicantia were noted, and one had a fresh corpus luteum.

Endometrial tissue was available for study in 22 cases. Varying degrees of proliferation and/or hyperplasia were noted, but carcinoma of the endometrium was not encountered in this series.

Results of operation

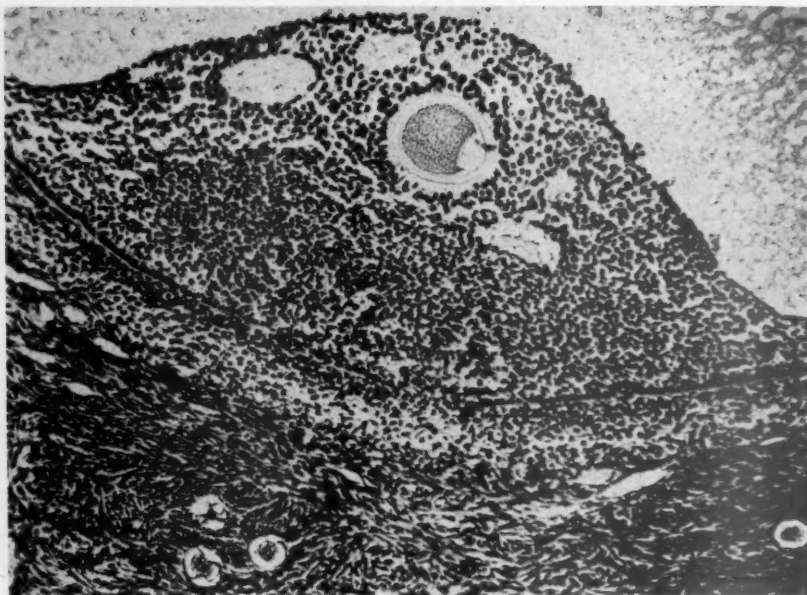
Following ovarian wedge resections, 36 of the 40 patients developed ovulatory cycles, and 21 had a total of 37 pregnancies. Three were operated on too recently to evaluate restoration of ovulation. Among those who have not conceived, 10 were operated on during the past year, 2 are unmarried, and one has an oligospermic husband.

Two had previous ovarian wedge resections elsewhere, and one of these has now conceived twice since the second operation.

Two of the patients who ovulated for a time following operation have since reverted to their original status. Review of these patients' histories, laboratory data, and treatment failed to disclose the cause of reversal. However, one of the patients had stopped supplemental thyroid therapy for established hypothyroidism some months previous to the return of anovulation and oligomenorrhea. Reinstitution of thyroid therapy has not yet improved ovarian function.

*The potency of the gonadotropin extracts was compared to that of Pergonal-23, a postmenopausal urine gonadotropin extract, obtained through the courtesy of Dr. Piero Donini, Serravallo Pharmaceutical Institute, Rome.

Fig. 3. Section of a follicle cyst at the site of the cumulus oophorus. Note the light-staining band of theca interna cells presenting a pseudo-lutein appearance ($\times 100$; reduced $\frac{1}{4}$.)



Results of endocrine investigation

All of the patients in this study had pre-operative excretory levels of estrogen and gonadotropin falling within our normal

ranges, except for rare isolated determinations (Tables I and II). The latter indicates the greater diagnostic value of serial assays over single determinations. With four excep-

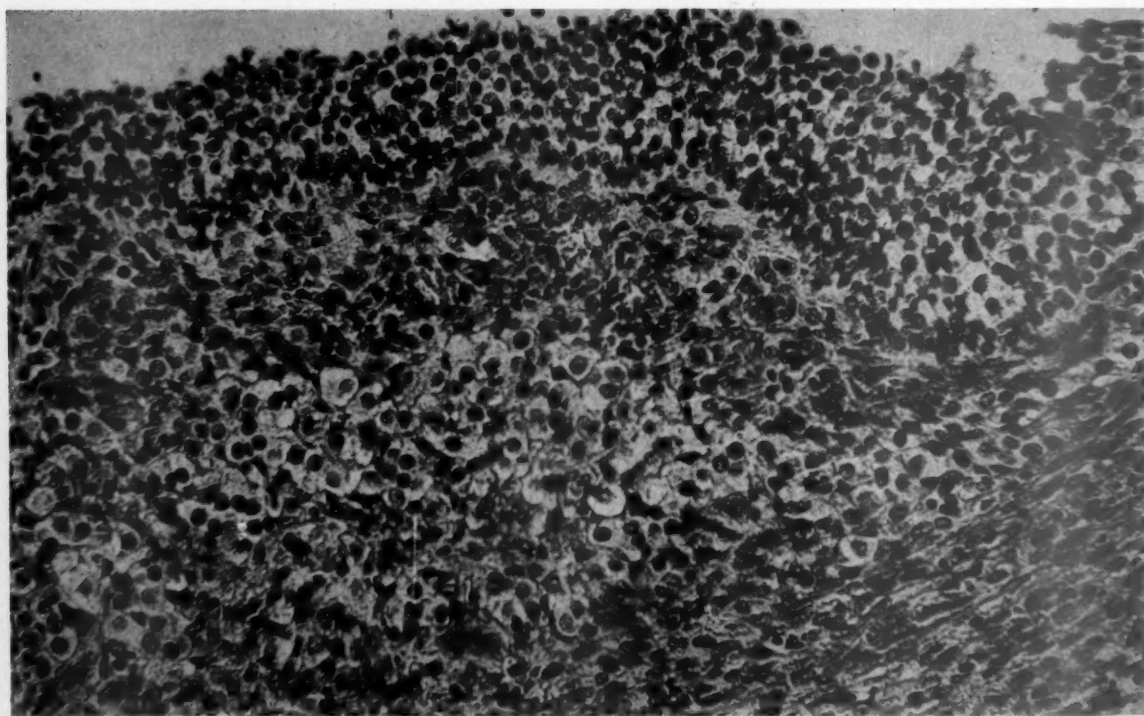


Fig. 4. Section of hyperplastic follicle from Patient J. L. (Fig. 5). Mitotic activity is present in both granulosa and theca interna layers. The histologic features of hyperthecosis are conspicuous. ($\times 140$.)

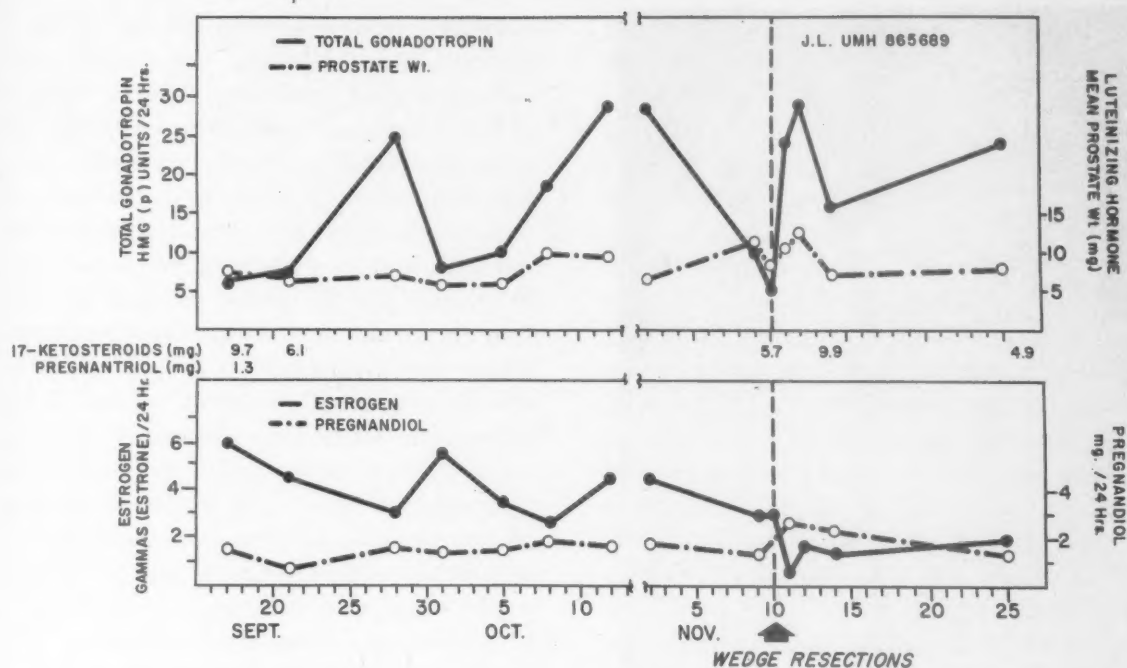


Fig. 5. Hormonal levels obtained pre- and postoperatively in a 22-year-old woman with polycystic ovarian disease. Basal temperature records and serial daily vaginal smears indicated ovulation followed by menstruation 7 weeks after operation.

tions, all patients had 4 or more estrogen and gonadotropin determinations, usually at weekly intervals, before operation. Daily vaginal smears were obtained, and a record of the basal body temperature was kept during the study period.

Sixteen patients had 17-ketosteroid excretion rates slightly elevated above the upper limits of the laboratory normal range (13 mg. per 24 hours). Repeat determinations revealed normal levels in 11 of the 16, including the 2 who were the only patients with values above 20 mg.

In 2 of the 3 patients tested for luteinizing hormone, the prostate responses of the hypophysectomized male rats were comparable to those obtained for 3 normal patients during the pre- and postovulatory phases. When the third patient with polycystic ovarian disease was tested, only slightly greater prostate weights were found. There appeared to be little difference between the preoperative and early postoperative excretion of LH.

Low levels of pregnanediol were obtained, and this was anticipated in the absence of

corpus luteum function. The small amounts of pregnanetriol recovered were compatible with the 17-ketosteroid levels and reflect

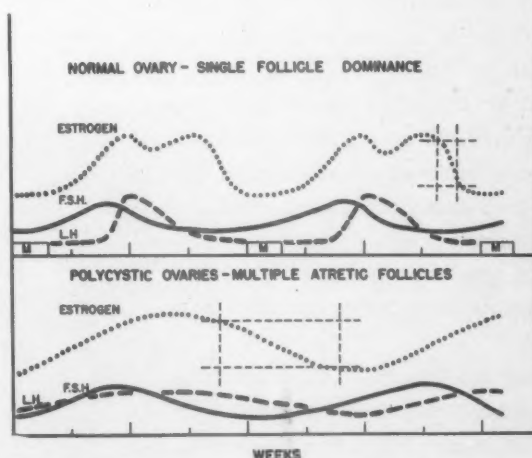


Fig. 6. Diagrammatic representation of fluctuations in estrogen and gonadotropin levels in patients with normal cycles and patients with polycystic ovarian disease. The slow reduction in estrogen (portion enclosed by dotted lines) may account for absent or infrequent menstruation characteristic of polycystic ovarian disease. The FSH curves represent total urinary gonadotropin since specific tests for FSH were not used.



Fig. 7A. Female rats in parabiosis. The animal on the left has been castrated, and the one on the right hypophysectomized.



Fig. 7B. Hypophysectomized female rat (left) in parabiosis with castrate female (right). Arrows indicate the markedly enlarged, cystic ovaries of the hypophysectomized animal.

relatively normal adrenal cortical function.

In Fig. 5 the immediate postoperative changes show the expected reciprocal relationship between estrogen and gonadotropin levels. However, there was some variability in the early postoperative levels in several patients, particularly with respect to estrogen excretion. The magnitude of estrogen depression may be related to the amount of estrogen-producing tissue removed, as well as to the impact of operative stress on adrenal cortical function. Three patients developed transient vasomotor menopausal symptoms soon after operation, but subsequently ovulatory cycles were established.

Progressive postoperative changes in the vaginal smears provided additional evidence of physiologic dominance of a single follicle and ovulation. Postoperative evaluation of daily vaginal smears and basal temperature records in 21 patients indicated the probability of the first ovulations occurring within 2 months of operation. Eight patients were pregnant within 3 months after wedge resection of the ovaries.

Interpretation of endocrine data

In Fig. 6 a comparison is made between the endocrine changes associated with normal menstrual cycles and a composite of the changes suggested by the endocrine studies from patients with polycystic ovarian disease. Although relatively normal levels are observed in the patients with polycystic ovaries, the more abrupt changes essential for ovulation and menstruation do not occur. Estrogen levels within the normal range are seen in the patients with polycystic ovaries, but the levels are more constant with the absence of peaks normally observed at time of ovulation, as well as the precipitous drop preceding menstruation.

Gonadotropin levels also fall within normal range, but with more fluctuation than that observed in the estrogen levels. In some the gonadotropin and estrogen excretion rates suggested an inverse or reciprocal relationship.

Lack of progesterone production in these patients is evident from the absence of

progestational changes in the endometrium and the low pregnanediol levels.

Low pregnanetriol levels in all patients tested suggest that adrenal cortical hyperplasia was not a factor in producing the polycystic ovarian changes.

Etiology

Since the original description of the Stein-Leventhal syndrome in 1935, various explanations of the origin of this disease have been advanced. Many have observed the thickened capsule of polycystic ovaries and have suggested that this may act as a physical barrier to ovulation. Stein and Leventhal¹³ postulated that an endocrine imbalance may lead to the disorder. Ingersoll and McDermott¹⁴ thought that the condition might result from abnormal LH production. Recent endocrine studies of Ingersoll and McArthur¹⁵ led these authors to conclude that the excretion of one or more gonadotropins fluctuates abnormally and periodically reaches high levels.

Keettel and his associates,¹⁶ using the response of the immature rat ovary as a physiological indicator, demonstrated a qualitative effect which suggested to them an excess of LH in 10 of 11 patients with polycystic ovaries. Furthermore, a remarkable response of the polycystic ovary to an FSH type gonadotropin was regarded as a reflection of an FSH deficiency. DuToit¹⁷ felt that derangement of the theca cone prevented normal follicle maturation and ovulation. Shippel¹⁸ attributed the ovarian changes to ovarian dysfunction resulting in anovulatory cycles with progression to theca cell dominance.

Attention has also been directed to the association of hirsutism with cystic change of the ovaries. Allen and Woolf¹⁹ called attention to the possible etiological role of androgen production by stromal cells of the medullary portion of the ovary. Gallagher and his associates²⁰ found elevated excretory levels of steroids believed to be derived from androgen precursors of adrenal origin. The appearance of hirsutism in almost 50 per cent of patients with polycystic ovarian disease in-

dicates that increased androgen production is an important component of this disease.

Review of our clinical material suggested that any condition associated with recurrent anovulatory cycles may lead to the development of polycystic ovaries. Such recurrent follicular phases without ovulation and corpus luteum formation are most common during puberty, menopause, postpartum periods, and, in some instances, in hypothyroidism. Since 2 patients were sisters, genetic factors may play a role.

Because analysis of the clinical and laboratory data did not identify the basic mechanism of production of polycystic ovaries, an evaluation of the experimental conditions necessary for the production of cystic ovaries was undertaken.

Duplication of the classic parabiont experiments of Witschi and Levine²¹ were carried out where female rats are joined skin to skin, one animal being castrated and the other hypophysectomized (Figs. 7A and 7B). The pituitary of the castrate produces gonadotropin which is primarily FSH which stimulates follicular growth and cystic ovarian change after passing into the circulation of the hypophysectomized parabiont (Figs. 8 and 9). When the experimental conditions are modified so that the noncastrate rat retains its pituitary, the estrogen produced by the follicles stimulates the pituitary to secrete LH and luteinization occurs.

Similar effects are produced by transplanting ovaries into the spleen.²² Estrogen is produced and, upon entering the portal circulation, is promptly inactivated by the liver. The anterior pituitary is then no longer regulated by estrogen and produces predominantly FSH, resulting in multiple follicle cysts in the transplanted ovaries.

Further observations were made in castrate male rats with ovarian renal transplants (Fig. 10). A number of such animals were treated with 2.5 I.U. of chorionic gonadotropin daily during the study period. The animals were killed from 27 to 95 days after ovarian transplantation. Surviving transplanted ovaries in untreated animals showed with rare exception only follicular development with typi-

cal cystic changes in many instances (Fig. 11). Surviving ovaries in animals treated with chorionic gonadotropin were markedly luteinized. The most arresting observation in this experiment was the significant increase in the weights of the adrenals of the animals with surviving ovarian transplants as compared with the adrenal weights of a control group of castrated rats, a group of intact male rats, and a group of adult female rats.

Collation of the clinical and experimental findings suggest that the development of polycystic ovaries may result from continued exposure of the ovaries to gonadotropic stimulation which is predominantly, but not exclusively, follicle stimulating in nature (Fig. 12). A succession of follicular phases, uninterrupted by ovulation and corpus luteum formation, results in an accumulation of atretic follicles. Depending on the stage of growth or regression, these follicles may include typical small cysts, maturing follicles with evidence of atresia, follicles showing hyperplasia of both granulosa and thecal layers, or follicles with marked hyperplasia of the theca interna layer.

The stimulated follicles produce estrogen in a relatively continuous manner still subject to a reciprocal relationship with pituitary gonadotropin production. This relationship is expressed by rising levels of gonadotropin resulting in increased secretion of estrogen until the level of estrogen is such that it depresses the output of gonadotropin. Lowered levels of gonadotropin will, in turn, be followed by a depression in estrogen production. Thus, the anterior pituitary ovarian cycle is completed. Characteristically, and presumably due to the failure of a single follicle to dominate the cycle, the fluctuations in gonadotropin and estrogen production are less dramatic than in a normal ovulatory cycle. While wide variations may be encountered over a period of time, sudden increases or depressions are not common.

Although the qualitative nature of the gonadotropin produced by patients with polycystic ovarian disease is not definitely known, a relative increase in LH has been

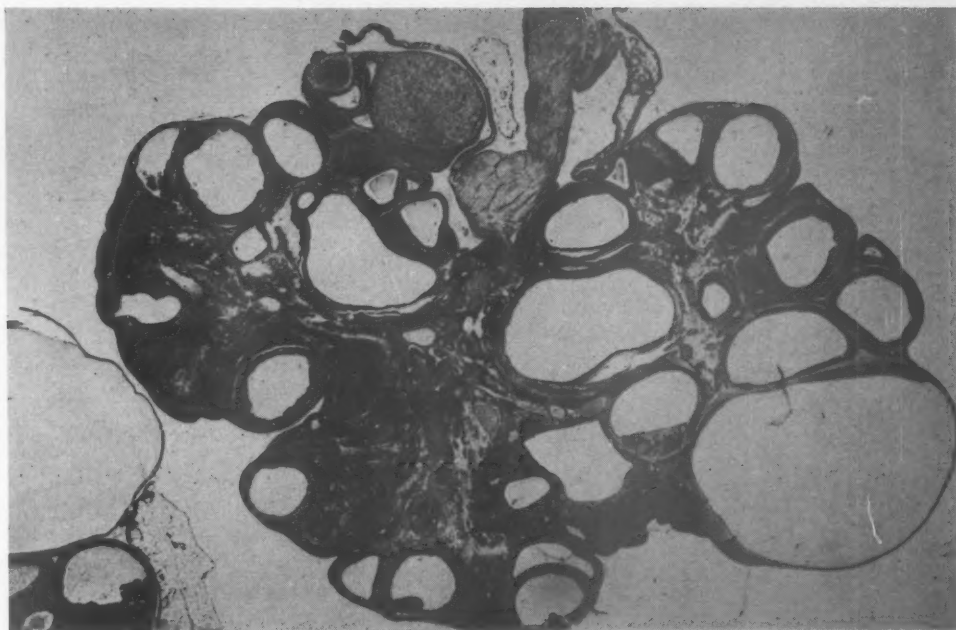


Fig. 8. Section of ovary from an hypophysectomized female rat after 47 days in parabiosis with a castrated female rat. The follicles show varying degrees of maturation and cystic degeneration. A single corpus luteum is present. Compare with the normal ovary illustrated in Fig. 9. ($\times 14$.)

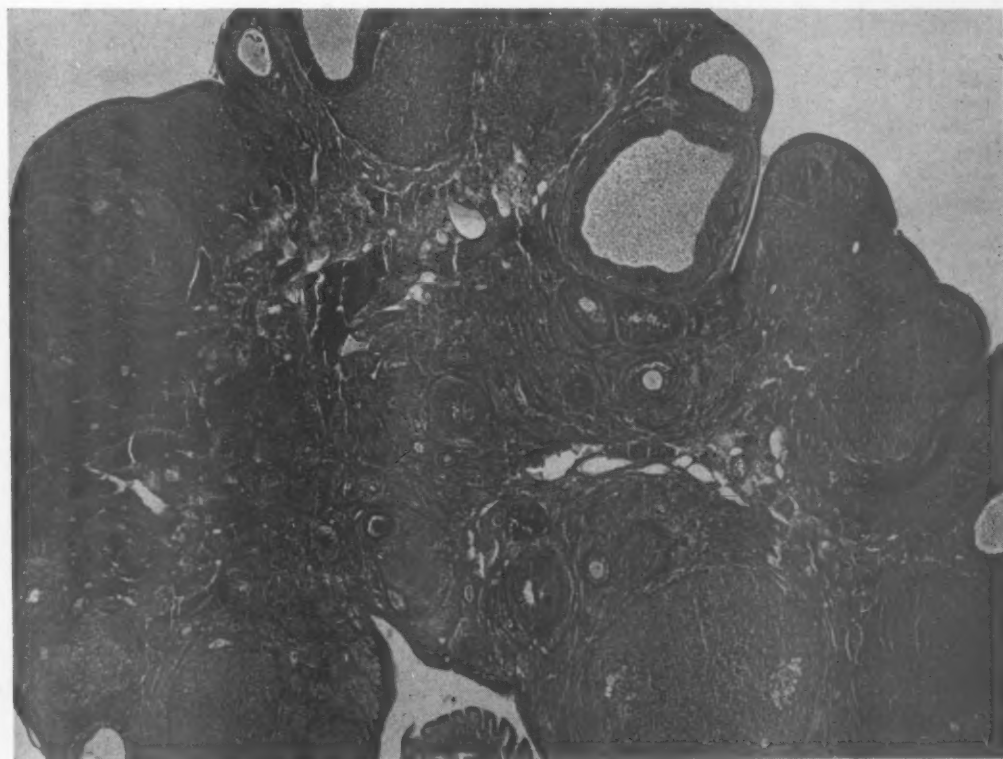


Fig. 9. Section of rat ovary at the diestrous phase of the ovarian cycle showing numerous corpora lutea and a few follicles. Compare with cystic ovary in Figs. 8 and 11. (Original magnification $\times 40$.)



Fig. 10. Cystic ovary growing beneath the renal capsule of a castrated male rat 74 days after transplantation.

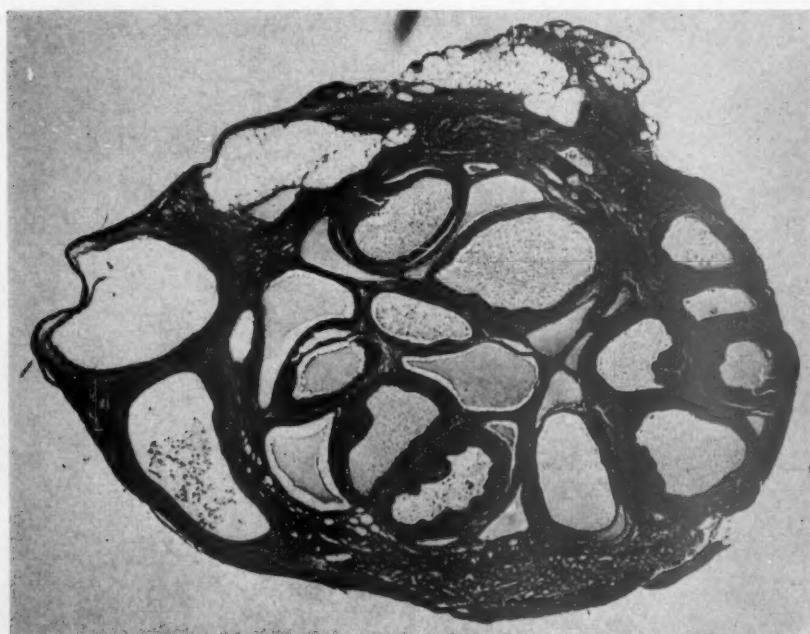


Fig. 11. Section of cystic rat ovary, 74 days following transplantation beneath the renal capsule of a castrated male rat. Most of the follicles show evidence of cystic degeneration. Compare with Fig. 9. ($\times 24$.)

suggested by Keettel and associates.¹⁶ However, lack of typical luteinization and absence of progesterone production suggest that LH production does not reach the level necessary for corpus luteum formation. If LH is increased to some extent, this may result in abnormal follicle maturation and hyperthecosis.

Although the anterior pituitary-ovarian relationships may be disturbed in patients with polycystic ovarian disease, the noted fluctuations in estrogen and gonadotropin excretion suggest that reciprocal relationships do exist.

This sequence of events may not apply to all cases of polycystic ovarian disease. For example, when these ovarian changes are associated with the adrenogenital syndrome, it is probable that the nature of the gonadotropin production is influenced by the increased adrenal production of sex steroids.

Although the impact of altered thyroid function upon the pituitary-ovarian axis is poorly understood, lowered thyroid activity may modify ovarian response to gonadotropin or influence the quality of gonadotropin produced by the pituitary. Such possibilities must be explored before any single explanation is entertained for the development of polycystic disease.

This endocrine sequence provides a basis for a more plausible explanation of the spectacular results of ovarian wedge resections (Fig. 13). Excision of many, but obviously not all, of the estrogen-producing cystic and atretic follicles results in a sudden reduction in estrogen. The resulting increase in gonadotropin stimulates a new crop of follicles with one destined for maturation without opposition of the estrogen from the excised atretic follicles. Thus, a more normal relationship is established between the pituitary and the ovaries. The success of wedge resections is dependent upon the creation of a physiologic environment which permits normal follicle maturation.

This sequence of events might be triggered by any operative procedure that removes or inactivates enough of the accumulated follicles. Removal of the thickened

capsule does not appear to be essential since, in the operative procedure described, it was carefully approximated after excision of a wedge. A more selective type of operative procedure does not seem indicated.

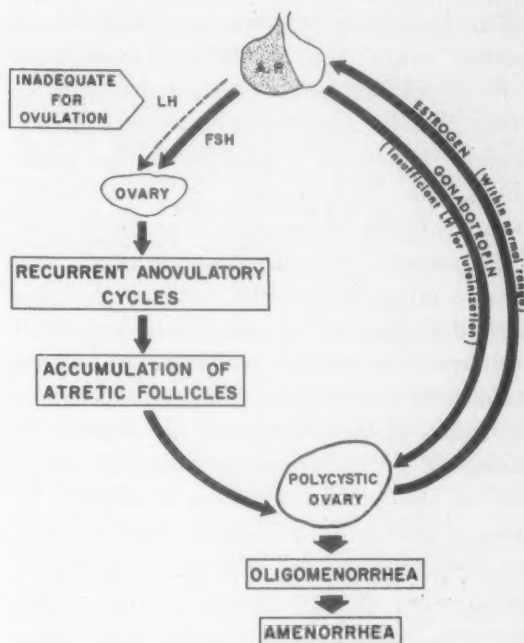


Fig. 12. Possible endocrine sequence leading to polycystic ovarian disease.



Fig. 13. Rationale for treatment by ovarian wedge resections.

The amount of estrogen in the cyst fluid was assayed in 4 patients. This revealed wide variation from undetectable amounts to the equivalent of one gamma per cubic centimeter of cyst fluid. Logically, there should be wide variation depending upon the functional status of the granulosa cells lining the cysts from which the fluid is removed.

This hypothesis still does not identify the missing "spark" that would induce ovulation in these patients before the accumulation of atretic follicles makes this infrequent or impossible. However, several intriguing possibilities arise. Would more aggressive endocrine treatment of patients at an early stage of anovulatory ovarian function, e.g., suppressive estrogen therapy, prevent the ultimate development of the Stein-Leventhal syndrome? When the syndrome is already established, would cyclic progesterone reduce the likelihood of development of endometrial carcinoma by interrupting prolonged exposure of the endometrium to estrogen? In young women with anovulatory ovarian function and excessive uterine bleeding unresponsive to other therapy, would ovarian wedge resections be an effective procedure? These are but several of the many questions that arise suggesting that the problem of polycystic ovarian disease is only a part or phase of the broad problem of anovulatory ovarian function.

Summary

Forty patients with a diagnosis of polycystic ovarian disease (Stein-Leventhal syndrome) are presented. All were subjected to ovarian wedge resections which resulted in ovulatory cycles in 36. Thirty-seven pregnancies occurred in 21 patients.

All had normal excretory rates for estrogen and gonadotropin. 17-Ketosteroid levels were normal or slightly elevated. In those cases tested, pregnanetriol values were all within normal limits. Pregnanediol levels were comparable to those found during the follicular phase of a normal menstrual cycle.

In 2 patients LH excretion was comparable to that found in three normal patients during the pre- and postovulatory phases. A third patient had slightly greater LH levels.

Cystic ovaries were produced experimentally in rats by several methods which permitted continuous exposure of the ovaries to FSH without sufficient LH for ovulation and luteinization.

Analysis of these clinical and experimental data provides a possible explanation for the production of polycystic ovaries and the usually favorable response to ovarian wedge resections. These observations suggest that the Stein-Leventhal syndrome is but a part or phase of the over-all problem of anovulatory ovarian function.

REFERENCES

1. Evans, T. N., and Riley, G. M.: *Obst. & Gynec.* 12: 168, 1958.
2. Dockerty, M. B., Lovelady, S. B., and Floust, G. T.: *AM. J. OBST. & GYNEC.* 61: 966, 1951.
3. Jackson, R. L., and Dockerty, M. B.: *AM. J. OBST. & GYNEC.* 73: 161, 1957.
4. Kaufman, R. H., Abbott, J. P., and Wall, J. A.: *AM. J. OBST. & GYNEC.* 77: 1271, 1959.
5. Klinefelter, H. F., Jr., Albright, F., and Griswold, G. C.: *J. Clin. Endocrinol.* 3: 529, 1943.
6. Riley, G. M.: *Gynecologic Endocrinology*, New York, 1959, Paul B. Hoeber, Inc., pp. 255-257.
7. McArthur, J. W., Ingersoll, F. M., and Worcester, J.: *J. Clin. Endocrinol.* 18: 460, 1958.
8. Gallagher, T. F., Peterson, D. H., Dorfman, R. I., Kenyon, A. T., and Koch, F. C.: *J. Clin. Invest.* 16: 695, 1937.
9. Allen, E., and Doisy, E. A.: *J. A. M. A.* 81: 819, 1923.
10. Dao, T. L.: *Endocrinology* 61: 242, 1957.
11. Robbie, W. A., and Gibson, R. B.: *J. Clin. Endocrinol.* 3: 200, 1943.
12. Eberlein, W. R., and Bongiovanni, A. M.: *J. Clin. Endocrinol.* 18: 300, 1958.
13. Stein, I. F., and Leventhal, M. L.: *AM. J. OBST. & GYNEC.* 29: 181, 1935.
14. Ingersoll, F. M., and McDermott, W. V.: *AM. J. OBST. & GYNEC.* 60: 117, 1950.
15. Ingersoll, F. M., and McArthur, J. W.: *AM. J. OBST. & GYNEC.* 77: 795, 1959.
16. Keettel, W. C., Bradbury, J. T., and Stoddard, F. J.: *AM. J. OBST. & GYNEC.* 73: 954, 1957.
17. DuToit, D. A. H.: *Polycystic Ovaries—Menstrual Disturbances and Hirsutism*, Leyden, 1951, Kroese.

18. Shippel, S.: *J. Obst. & Gynaec. Brit. Emp.* 6: 321, 1955.
19. Allen, W., and Woolf, R. B.: *AM. J. OBST. & GYNEC.* 17: 826, 1959.
20. Gallagher, T. F., Kappas, A., Hellman, L., Lipsett, M. B., Pearson, O. H., and West,

C. D.: *J. Clin. Invest.* 37: 794, 1958.

21. Witschi, E., and Levine, W. T.: *Proc. Soc. Exper. Biol. & Med.* 32: 101, 1934.
22. Li, M. H., and Gardner, W. U.: *Cancer Res.* 7: 549, 1947.

Discussion

DR. ROGER B. SCOTT, Cleveland, Ohio. Until one has had the opportunity of reading the published paper in full, he can have little concept of the thoroughness of this study. For example, Patient 31 preoperatively had sufficient repeats of the 5 endocrine assays to total 50 determinations. The wide weekly fluctuations of the results in many instances is an example of the unreliability of any single endocrine assay.

Unfortunately, there has been a rather generalized trend to lump various entities associated with episodes of absence of ovulation under the general syndrome of "Stein-Leventhal syndrome" or "polycystic ovarian disease." Stein and Leventhal emphasized an essential feature of their syndrome, i.e., enlarged polycystic ovaries. It is disturbing to me to know that in this series, 10 patients did not have enlarged ovaries and an additional 25 had ovaries "4 cm. or less" in diameter, a size hardly worthy of the term "slightly enlarged."

The essayist's findings indicating insufficient LH production for luteinization are at variance with those of Keettel, Bradbury, and Stoddard and Ingersoll and McArthur. Keettel and his associates used an assay method involving the response of the immature rat ovary, but the technique used by Ingersoll and McArthur measured the response of the prostate of the immature, hypophysectomized male rat, similar to the method used by Drs. Evans and Riley. If possible, this discrepancy should be explained.

By their preoperative endocrine assays they can reasonably well exclude any patient from their study with pituitary failure, primary ovarian failure, virilizing adrenal hyperplasia, or virilizing adrenal or ovarian tumors. Similar assay results can be found in other conditions associated with anovulatory cycles, with or without abnormal bleeding or amenorrhea, such as in the immediate postmenarche years, postpartum, and premenopausally.

The triggering mechanism which initiates the typical Stein-Leventhal syndrome still defies recognition. An occasional ovulatory cycle is compatible with this condition, but does not cure it. The authors' concept of wedge resection re-

sponse as one initiated by the excision of a sufficient number of estrogen-producing follicles may be tenable, but I am not particularly happy with it.

I wrapped the ovaries of monkeys with colloidion or dicetyl phosphate impregnated polyethylene film. The formation of corpora lutea was not inhibited. Also, the work reported one year ago by Scott and Wharton on the effect of testosterone on experimental endometriosis in monkeys showed an interesting side effect—thickening of the ovarian tunica.

Detailed fractionation of the urinary 17-ketosteroids in patients with this syndrome have indicated relative excesses of androsterone and etiocholanolone. These particular fractions may be diminished by small doses of cortisone. Has the essayist any experience with such fractionation or the clinical response to cortisone of any of his patients whose ovaries were not enlarged?

The authors of this paper seem a lot closer to an explanation of the etiology than were the writers of an article appearing in a recent issue of a Brazilian journal: "... a psychoneuroendocrine condition involving a feeling of insecurity and a desire to be a man. This feeling causes, through a corticohalamohypothalamic axis, a disorganization of the basophil system in the anterior lobe of the hypophysis, which is responsible for the ovarian and adrenal alterations in this syndrome."

DR. EVANS (Closing). There does not appear to be a marked disparity in our luteinizing hormone levels as compared with those reported by McArthur, Ingersoll, and Worcester. The prostate response noted by them was somewhat higher than that observed in 2 of the 3 patients we tested. It is of interest that their levels of luteinizing hormone in patients with the Stein-Leventhal syndrome were comparable to those found in a patient with amenorrhea secondary to rudimentary ovaries.

Dr. Scott's experimental work in wrapping the ovaries in an effort to prevent corpus luteum development probably is not entirely analogous to the situation existing in polycystic ovarian disease. The serial endocrine changes associated

with polycystic ovaries seem to be incompatible with ovulation. Probably the thickened capsule is not a significant barrier but only a secondary endocrine effect comparable to that observed by Dr. Scott in monkeys receiving injections of androgen, reported before this Society last year.

We have not subjected our patients with normal levels to fractionation of 17-ketosteroids. In

the few patients treated preoperatively with cortisone, we were unable to detect ovulation. We would not anticipate a favorable response to cortisone in those patients with normal 17-ketosteroid excretion rates. However, this may prove to be a rational procedure before operation is resorted to, especially in those patients with elevated levels.

Metabolism of estrone-C¹⁴-16 sulfate in women

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FOR many years sodium estrone sulfate has been used in the hormonal treatment of women. It is the principal estrogenic constituent of pregnant mare's urine, constituting over 60 per cent according to the work of Grant and Beall.¹ The usual form in which it is used clinically is as a somewhat refined and concentrated preparation of pregnant mare's urine (marketed under the trade name of Premarin). Since it is water soluble, sodium estrone sulfate can be given freely by the intravenous route; Hertz² reported that he had administered as much as 2,400 mg. to a male patient in 14 hours without ill effect.

Schacter and Marrian³ were the first to show that estrone sulfate occurred in pregnant mare's urine when they isolated it as the potassium salt in 1938. In 1939 estrone sulfate was synthesized from estrone by Butenandt and Hofstetter,⁴ who described its properties and postulated that it probably was the form in which estrogens were excreted in human urine. In this they were wrong since most of the estrogenic steroids are excreted as esters of glucuronic acid, as demonstrated by Beer and Gallagher,^{5, 6} who used large and small doses of radioactive 17 β -estradiol-16-C¹⁴.

Very few papers have appeared on the absorption, metabolism, physiological action,

or excretion of estrone sulfate. Material labeled with radioactive S³⁵ was made available in 1950, and some experiments were performed, by us and by others, on its possible localization in tissues. Three papers were published. One by Lewison and associates⁷ showed that most of the radioactive sulfur was broken off promptly and appeared in the urine of injected rats, although 6 to 8 per cent remained as estrone sulfate. In 8 patients with cancer, an average of 80 per cent of the radioactive sulfur appeared in the urine in 72 hours, of which 6 to 25 per cent may have been estrone sulfate. Various tissues measured for radioactivity showed less than that found in the plasma, except for breast cancer which showed 2½ times the concentration in the plasma, and cervical mucosa, roughly twice as radioactive as the plasma.

Hanahan and Everett,^{8, 9} on the other hand, found considerable amounts of S³⁵ in the feces of injected rats and were unable to demonstrate any unhydrolyzed estrone sulfate in either urine or feces. No tissue localization of S³⁵ was found. In pregnant rats no radioactivity crossed the placental barrier. The sulfatase involved in hydrolysis of the estrone sulfate seemed to come from the liver as indicated by experiments with tissue homogenates.

Davis and co-workers¹⁰ reported finding some evidence of tissue localization of S³⁵ at 15 minutes after intravenous injection in kidneys, liver, and genital tract, but none at later intervals. They also found evidence of rapid hydrolysis in the body but were able, unlike Hanahan and Everett, to re-

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cover unhydrolyzed estrone sulfate from both urine and feces.

Only Lewison and his co-workers carried on their experiments in human subjects. This is a pity, for certainly it is easily demonstrated that the steroid metabolism of one species often bears no relationship to that of another.

The labeled hormone used in these experiments was labeled only in its sulfate side chain. Consequently, the observations could not be correlated with the fate of the truly important estrone nucleus.

In 1959, Purdy, Engel, and Oncley¹¹ reported that patients injected with estradiol-16-C¹⁴ showed labeled estrone sulfate in their plasma and that this constituted the principal circulating human estrogen. These observations have been reported in greater detail by Purdy,¹² who found 69 to 73 per cent of all the radioactive estrogens in the plasma to be estrone sulfate and only 5 per cent to be estrone glucuronate 2½ hours after the intravenous administration of estradiol-16-C¹⁴. In plasma obtained from women in the third trimester of pregnancy, Purdy found unconjugated estrone, estradiol, and estriol in concentrations of 11, 10.6, and 0.8 µg per liter compared with 52.4 µg of sodium estrone sulfate. These figures which represent endogenous hormone plasma levels were determined by isotopic dilution methods.

Sandberg and Slaunwhite¹³ reported observations on the transport of estrogens by the plasma after intravenous injection of C¹⁴ estrone and estradiol. Their observations, made in 1957, are at variance with those of Purdy in that they found one third as much sulfate as glucuronide in the plasma. Migeon, Wall, and Bertrand¹⁴ have confirmed Sandberg and Slaunwhite's findings, except that they believe the glucuronide fraction in the plasma to be even higher.

In interpreting these conflicting results it must be noted that the two groups of investigators used totally different methods of analysis. Purdy and associates¹¹ fractionated the plasma according to Cohn Method 6,¹⁵ extracted the fractions with Delsal's

reagent and added carrier sodium estrone sulfate and estrone glucuronic acid which they separated by chromatography and countercurrent distribution. When constant specific activity had been obtained, the original content of the esters was calculated.

Sandberg and Slaunwhite,¹³ and Migeon, Wall, and Bertrand¹⁴ hydrolyzed the plasma with β-glucuronidase and extracted with ether. All material which was made soluble by this procedure was presumed to be glucuronide, an assumption open to some criticism. At least one can say that Purdy's work makes the occurrence of the estrogens in human blood chiefly as estrone sulfate a likely possibility.

Our interest in the properties of sodium estrone sulfate was aroused during some studies on the transfer of estrogens in the blood of the guinea pig from mother to fetus. When estrone was injected into the mother, water soluble conjugates appeared almost immediately in maternal and fetal circulations. However, further investigations showed that this was due to penetration of the placental barrier by free estrone and its conversion by fetal tissues, as well as by maternal tissues, into estrogen conjugates. Sodium estrone sulfate made radioactive at Position 16 with C¹⁴ did not appear in the fetus when perfused in the mother.¹⁶

Having provided ourselves with labeled estrone sulfate, we felt that it would be simple to carry on experiments on patients to determine the absorbability of this material when taken by mouth as compared with estrone, to follow its metabolism in the body, to study its metabolic products in the urine, and perhaps even to study its localization in various organs.

Material and methods

Sodium estrone-16-C¹⁴ sulfate was synthesized by treating estrone-16-C¹⁴ with chlorosulfonic acid in pyridine, the method used originally by Butenandt and Hofstetter.⁴ The estrone used had an activity of 22 µc per milligram. The sodium estrone sulfate, as used, was of two radioactive specific activities, 3.5 µc and 15.4 µc per milligram.

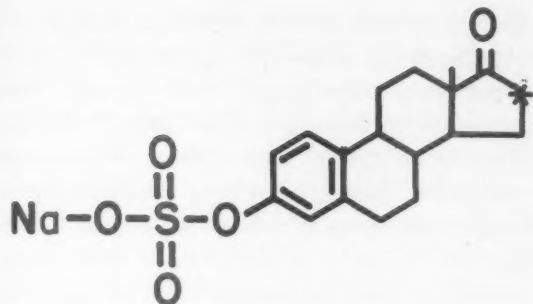


Fig. 1. Sodium estrone-16-C¹⁴ sulfate (18,400,000 counts per minute per milligram).

In our counting devices, an automatic thin window counter and a D 46A windowless flow gas counter, the lower activity hormone gave 2.1 and 9.2 million and the higher activity material 4.2 and 18.4 million counts per minute per milligram, the higher counts being in the more sensitive windowless counter (Fig. 1). For purposes of uniformity, we have recorded all our data on counts per minute as though they were measured in the latter device.

To determine the purity of the sodium estrone sulfate the material was chromatographed on paper. It was also hydrolyzed with phenolsulfatase, extracted with ether, and chromatographed on paper in parallel with authentic estrone. These studies showed the material to be authentic and of reasonable purity.

In preparing the hormone for patient use the pyridine solution of estrone sulfate was treated with sodium hydroxide and the pyridine removed under reduced pressure. The sodium estrone sulfate was extracted with butanol. The butanol was removed by drying and the salt dissolved in normal saline. The saline solution was first assayed for radioactivity and then kept frozen as a standard solution. When patients were to be given the hormone by mouth, the solution was thawed out and an aliquot pipetted into a tumbler, diluted with water, and given to the patient to drink. The tumbler was refilled twice with water, the patient drinking the washings, to insure complete consumption of the entire dose.

If the sodium estrone sulfate was to be given intravenously, the stock solution was

filtered in carefully measured amount through a sintered glass ultrafine bacterial filter. The filter was washed with normal saline and the sterile hormone solution so obtained drawn up in a syringe for injection. The usual volume of solution injected was from 4 to 6 c.c.

The dose of radioactive carbon given to each patient was 1.3 to 10.8 μ c. This is well below the limit set by the Atomic Energy Commission as being permissible for normal subjects who receive only one dose.

Patients

The experiments to be reported fall into four different categories. In the first set, 3 normal women were given radioestrone sulfate by mouth and urine collected at hourly intervals for 48 hours thereafter.

This group was compared with a second group of 3 who were given radioactive estrone. The estrone was dissolved in peanut oil and enclosed in a gelatin capsule for administration by mouth. The doses given were 1 to 1.98 mg. containing 5 to 10.8 μ c. Again hourly collections of urine for 48 hours were made.

The third group consisted of 3 women with biliary fistulas following cholecystectomy. These were patients of Dr. Arthur Localio whose help and cooperation we wish to acknowledge gratefully. Each patient had a T tube in the common bile duct. Each had been operated upon more than 3 days before our observations were begun. Each had an inlying Foley catheter for immediate complete collection of urine. In these women radioestrone sulfate was given by mouth in 7 μ c doses, and collections of bile and urine made at 5, 10, 15, and 30 minutes, at 1 hour, 2, 3, 4, 6, 9, 12, 18, 24 hours, and at 6 hour intervals thereafter for another 24 hours.

The fourth group consists of 4 who received radiosodium estrone sulfate intravenously. Two of these had urine collections at 24 hour intervals for 72 hours to determine the rate of excretion of the radioactive material. The other two were placed on constant urinary drainage. The radioactive so-

dium estrone sulfate was injected into the antecubital vein of one arm and samples of blood drawn from the other. These were heparinized. Blood and urine samples were taken at 5, 10, 15, and 30 minutes and at 1, 2, and 4 hours.

Treatment of urine, bile, and blood

Most of the urine samples were counted without extraction by plating 0.2 c.c. onto a tin-plated planchet and evaporating to dryness.

When it was desired to determine in what form the urinary metabolites were excreted, the urine was extracted with butanol by repeated shaking in a separatory funnel at pH 3. The butanol was removed under vacuum and replaced with water. Aliquots of the aqueous solution were hydrolyzed separately with β -glucuronidase and with sulfatase. For glucuronides, samples were treated with 500 Fishman units per milliliter at 37° C. and pH 5 for 24 hours with β -glucuronidase.* In each analysis, controls with no enzyme and with the specific β -glucuronidase inhibitor, saccharolactone, were run concurrently. The radioactive material extracted by ether after such enzyme treatment was considered to have been present originally as glucuronide.

The aliquots on which sulfates were to be determined were treated with phenolsulfatase,† 1 mg. per milliliter at 50° C. and pH 6 for 24 hours. Controls with no enzyme and with phosphate, a phenolsulfatase inhibitor, were run concurrently. After the incubation, the solutions were extracted with ether and the radioactivities determined. Again, radioactivity made extractable with ether after sulfatase treatment was considered to have been present in the urine originally as sulfate.

For identification of the components in each of the above glucuronide and sulfate fractions further treatment was carried out.

This consisted first in chromatography on a column of silica gel.¹⁷ The "less polar" metabolites were eluted with 2 per cent methanol in benzene. The "polar" metabolites were eluted with 4 and 8 per cent methanol. Each of these fractions was further chromatographed on paper.¹⁸ For the "less polar" metabolites the paper was soaked in formamide and the descending chromatogram developed with benzene. On parallel strips nonradioactive estrone, estradiol, and 16-ketoestradiol were chromatographed simultaneously. The identity of the radioactive metabolite with the reference material was determined by showing that the location of the radioactive material on the paper, i.e., its distance from the point of application, or R_f , was the same as that of the nonradioactive steroid on the parallel paper as shown by spraying with Turnbull's blue.¹⁹

The "polar" metabolites were chromatographed on paper soaked in formamide and developed with chloroform. The reference steroids were 16-epiestriol and estriol.

Bile samples were treated in the same way as were urine samples. Assays were made on 0.2 ml. samples or on 0.02 ml. samples when the radioactivities were sufficiently high. When it was desired to determine in what form sodium estrone sulfate was excreted, the bile was extracted by shaking repeatedly with butanol. This procedure was found to remove the radioactive material almost quantitatively. Emulsions usually formed but these could be broken by centrifuging.

Attempts to hydrolyze estrogens in bile with β -glucuronidase directly were not very successful, probably because there is something in the bile which inhibits the enzyme activity. However, after extraction with butanol, removal of the butanol under vacuum, and redissolving of the conjugates in water, the inhibition seemed to disappear completely, and we were able to fractionate into glucuronides and sulfates with ease.

No attempt was made to chromatograph the bile and determine what changes had taken place in the steroid nucleus.

Blood samples were treated by separation

*Ketodase, Warner-Chilcott Laboratories, Morris Plains, New Jersey.

†Mylase P, Wallerstein Laboratories, New York, New York.

of plasma and red cells by centrifugation with subsequent precipitation of the plasma with alcohol-water (4 parts to 1). The red cells were discarded. The precipitated plasma was washed with 1:1 acetone-alcohol mixture. The alcohol and acetone-alcohol extracts were combined, dried in vacuo, and redissolved in water. Enzyme studies were carried out on this solution.

Results

When sodium estrone sulfate was given by mouth, radioactivity appeared in the urine at the end of 30 minutes and rose slowly to a maximum at around 24 hours. There was no well-marked peak of excretion. At the end of 24 hours 25 to 30 per cent of the radioactivity had appeared in the urine. At 48 hours 55 per cent had been excreted. There was still considerable radioactivity in the last specimen, but further excretion was not followed.

In contrast, radioactive estrone in oil given by mouth is absorbed to a much smaller degree. In the first 24 hours, 4.1, 3, and 7.7 per cent of the administered radioactivity appeared in the urine. At 48 hours, the second patient had excreted 5.7 per cent, the third 15.6 per cent; the last patient excreted a total of 17.1 per cent in 5 days (Fig. 2).

When the urine of one of the patients who had received radiosodium estrone sulfate

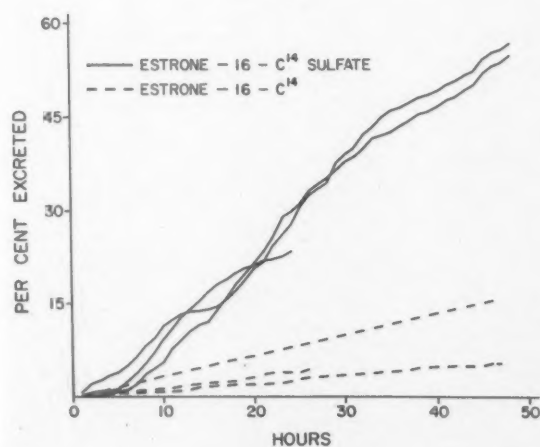


Fig. 2. Urinary radioactivity excreted by patients receiving estrone-16-C¹⁴ sulfate and estrone-16-C¹⁴.

Table I. Radioactive urinary conjugates excreted by patient receiving estrone-16-C¹⁴ sulfate intravenously*

Time	Excreted (c.p.m.)	% sulfates	% glucuronides
5-30 minutes	84,000	96	2
30-60 minutes	64,000	45	42
60-120 minutes	103,000	27	45
20-34 hours	327,000	2	47

*Patient received 3.9×10^6 counts per minute.

was fractionated, estrone, estradiol-17 β , estriol, 16-epiestriol, and ring D ketols were found in the glucuronide fraction of the urine obtained from 3½ to 24 hours after administration. The glucuronide fraction contained 86 per cent of the total radioactivity. The sulfate fraction contained only 4 per cent.

In contrast to this, the first 3½ hours' excretion of urine contained only estrone and estradiol in the glucuronide fraction. The radioactivity in this early excretion specimen was 56 per cent glucuronides and 6.5 per cent sulfates.

When sodium estrone sulfate was given intravenously, the urinary metabolites were also predominantly the glucuronides of estrone, estradiol-17 β , epiestriol, estriol, and ring D ketols (Fig. 3), but it was possible in this specimen to analyze the sulfate fraction also. This was found to contain estrone, estradiol-17 β , and ring D ketols in small amounts. No 16-epiestriol was detected, and only a small trace of estriol was found (Fig. 4). The glucuronide fraction contained 60 per cent of the excreted radioactivity and the sulfate fraction 1.3 per cent.

When sodium estrone sulfate was given by mouth to patients with biliary fistulas, radioactivity appeared simultaneously in the bile and in the urine between 15 and 30 minutes after administration (Fig. 5). After 30 minutes the radioactivity rose rapidly to reach a peak in both bile and urine at 5 hours. It then fell gradually but was still not entirely gone at 48 hours.

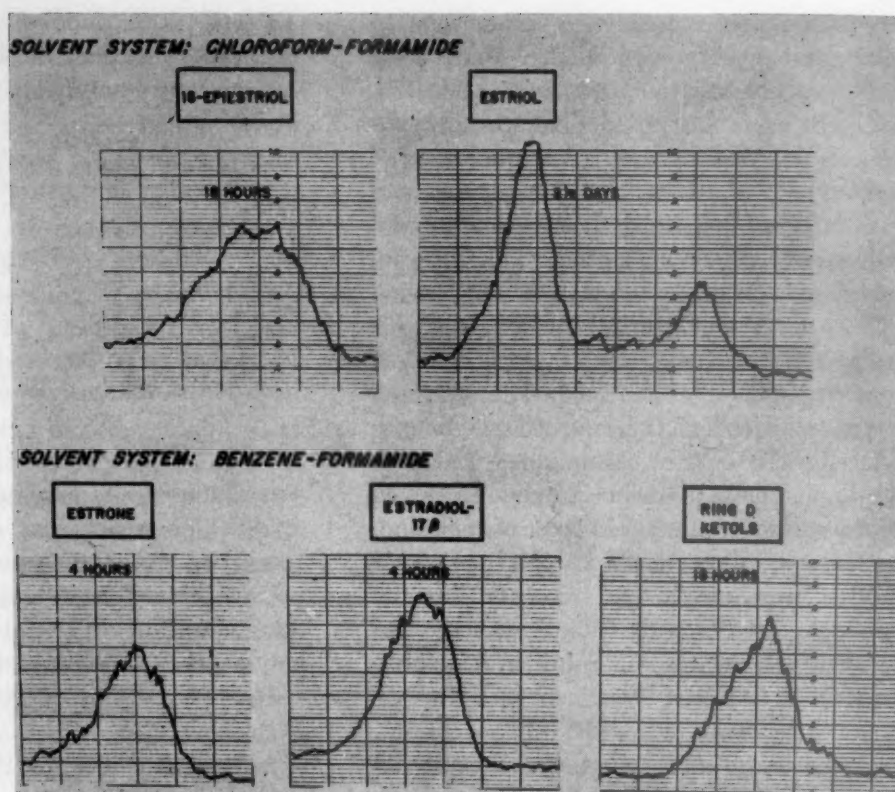


Fig. 3. Paper chromatograms of urinary metabolites (glucuronide fraction) of estrone-16-C¹⁴ sulfate 24 hours after intravenous injection.

Approximately equal quantities were excreted in bile and urine. In one patient biliary and urinary radioactivity added up to 106 per cent of injected counts; in an-

other, 83 per cent in 48 hours. It should be noted that these results are much higher than the total recovered activity in intact patients, 55 per cent in 48 hours, probably

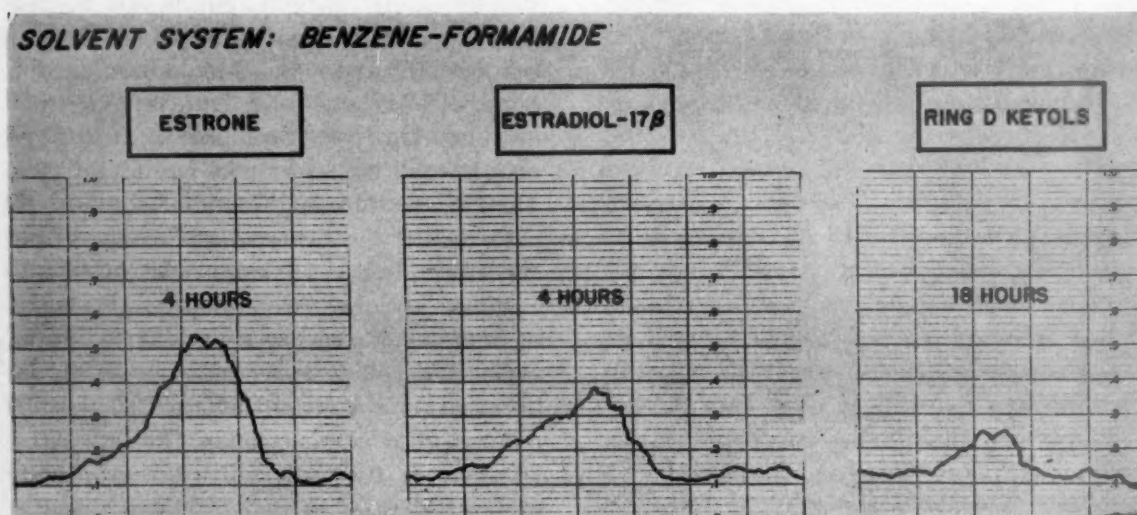


Fig. 4. Paper chromatograms of urinary metabolites (sulfate fraction) of estrone-16-C¹⁴ sulfate 24 hours after intravenous injection.

because in such patients the biliary activity must be absorbed and gradually eliminated in the urine.

Bile was fractionated to find out whether the metabolites in it were glucuronides or sulfates. In a specimen of bile gathered from 30 minutes to 2 hours after ingestion of sodium estrone sulfate-16- C^{14} by mouth, glucuronides constituted 32 per cent and sulfates 28 per cent.

When sodium estrone sulfate was given intravenously, approximately 44 per cent of the radioactivity was found in the urine in 24 hours. During the second day, an average of 21 per cent was recovered from the urine and in the third day, 8 per cent. In the first 30 minutes most of the radioactivity was in the form of the sulfate, 96 per cent (glucuronide 2 per cent), whereas from 20 to 34 hours after injection, only 2 per cent of the radioactivity in the urine appeared as sulfate and 47 per cent as glucuronide (Table I).

In 2 patients injected intravenously from whom repeated blood samples were drawn, only 15 per cent of the radioactivity expected by calculation was found in the plasma at 5 minutes. Eighty-five per cent had disappeared into the tissues or elsewhere. That this radioactivity was not in the urine is shown by Fig. 6, which indicates that even at the end of 4 hours only a total of about 15 per cent had been excreted.

The radioactivity of the plasma continued to fall for 15 minutes after injection at which point it stabilized at about 3 per cent of the calculated dose per milliliter and changed very little in the course of the next 4 hours.

Comment

The first two groups of patients clearly demonstrated that sodium estrone sulfate when given by mouth gets into the circulation and is finally excreted in the urine in much larger quantities than does estrone dissolved in oil administered by the same route. This certainly seems a reasonable explanation for the observed clinical effectiveness of this material.

It is certainly true that sodium estrone sulfate is excreted in the urine in the same forms and in approximately the same proportions as are estradiol-17 β and estrone.²⁰ These observations suggest that the sulfate is broken off somewhere in the passage of this material through the body, and the estrone part converted into estradiol, estriol, and other metabolites as would be injected

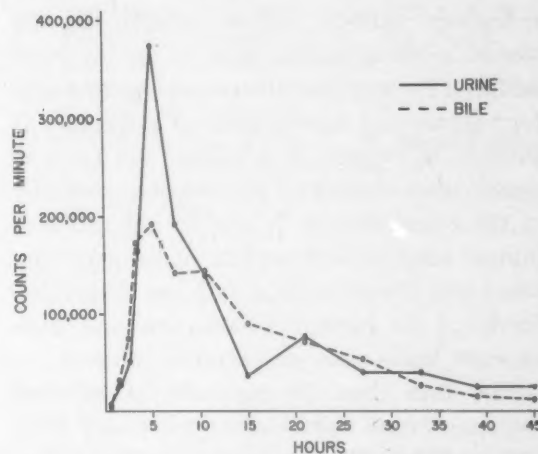


Fig. 5. Hourly excretion rate, counts per minute, in Patient R. M., common duct drainage, sodium estrone-16- C^{14} sulfate; given by mouth.

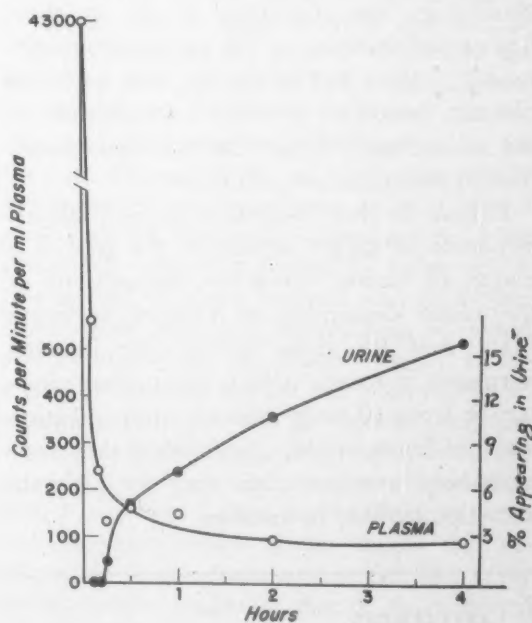


Fig. 6. Sodium estrone sulfate-16- C^{14} intravenously.

estrone itself. Where this hydrolysis takes place we do not know. At least considerable quantities of sulfate can pass through the liver apparently unchanged (28 per cent in one determination). Other observations, not detailed here, suggest that later samples of bile have a much higher proportion of glucuronide. In any case, it looks as though once sodium estrone sulfate is absorbed into the blood stream, it becomes indistinguishable from estrone and estradiol-17 β .

Sodium estrone sulfate labeled in the steroid nucleus would seem to be the ideal material for studying the physiological transformations and localizations of estrogens. If Purdy¹² is correct, it is indeed the form in which most estrogens are carried normally in the blood stream. It can be injected into human subjects without fear of damage even when put into the blood in large quantities. Study of its further localization and conversions waits only on suitable subjects.

The fact that 85 per cent of injected sodium estrone sulfate disappears in 5 minutes and that the corresponding radioactive carbon cannot be found in the urine for the next 3 days certainly suggests strongly that the material must be fixed in some bodily tissue with great rapidity. Preliminary studies in our laboratory seems to show higher radioactivity in the endometrium, for example, than in the plasma and, as noted already, Lewison⁷ discovered localization of the sulfate-labeled material in breast cancer. The implications are attractive.

It may be that the failure to find labeled estrogens in target organs in the past is a matter of timing. Since the radioactivity of the blood diminishes so rapidly, it seems likely that the time to look for injected hormones in ovary, breast, adrenal, or pituitary is from 10 to 30 minutes after injection and not hours or days later when they may have been sent on their way for ultimate excretion by liver or kidneys.

Gastrointestinal absorption, on the other hand, takes longer than we had expected, with little material coming through the liver or kidneys in less than an hour. The enterohepatic circulation of estrogens is amply reaffirmed in our observations. At least as much radioactivity appears in the bile as in the urine and must thereafter be subject to reabsorption by the intestine in the normal subject. This probably explains the prolonged excretion rate observed for this and all estrogens.

Summary

1. Radioactive sodium estrone sulfate has been synthesized with C¹⁴ at Position 16 in the steroid nucleus. Material has been used giving up to 18.4 million counts per minute per milligram in a windowless glow gas counter.

2. Comparative studies of urinary excretion of radioactive metabolites in patients taking this material by mouth with others taking radioactive estrone in oil show a much higher absorption of sodium estrone sulfate than of estrone. Fifty-five per cent of the ingested radioactivity appears in the urine at 48 hours, compared to 16 per cent or less for estrone.

3. Sodium estrone sulfate and estrone produce the same kind of metabolites in the urine in roughly the same quantities, suggesting that they are interconvertible within the body.

4. Sodium estrone sulfate given by mouth appears soon thereafter in the bile and in the urine. The quantities excreted by each route are roughly the same. At first the excretory products contain considerable sulfate. Later, they are largely glucuronides.

5. Sodium estrone sulfate injected into the body disappears very rapidly and probably becomes localized somewhere in the tissue.

REFERENCES

1. Grant, G. A., and Beall, D.: In Pincus, Gregory, editor: *Recent Progress in Hormonal*

Research, ed. 5, New York, 1950, Academic Press, Inc., pp. 307-334.

2. Hertz, R.: In Pincus, Gregory, editor: *Recent Progress in Hormonal Research*, ed. 5, New York, 1950, Academic Press, Inc., p. 328.
3. Schacter, B., and Marrian, G. F.: *J. Biol. Chem.* 126: 663, 1938.
4. Butenandt, A., and Hofstetter, H.: *Hoppe Seyler's Ztschr. physiol. Chem.* 259: 222, 1939.
5. Beer, C. T., and Gallagher, T. F.: *J. Biol. Chem.* 214: 335, 1955.
6. Beer, C. T., and Gallagher, T. F.: *J. Biol. Chem.* 214: 351, 1955.
7. Lewison, E. F., Levi, J. E., Jones, G. S., Jones, H. W., and Silverstein, H. E.: *Cancer* 4: 537, 1951.
8. Hanahan, D. J., and Everett, N. B.: *J. Biol. Chem.* 185: 919, 1950.
9. Hanahan, D. J., Everett, N. B., and Davis, C. D.: *Arch. Biochem.* 23: 501, 1949.
10. Davis, M. E., Kelsey, F. E., Fugo, N. W., Loucks, J. E., Horner, E. N., and Voskuil, P.: *Proc. Soc. Exper. Biol. & Med.* 74: 501, 1950.
11. Purdy, R. H., Engel, L. L., and Oncley, J. L.: *Fed. Proc.* 18: 305, 1959.
12. Purdy, R. H.: *Chemical Studies of Some Human Plasma Estrogens*, Dissertation for Ph.D., Harvard University, 1959.
13. Sandberg, A. A., and Slaunwhite, W. R., Jr.: *J. Clin. Invest.* 36: 1266, 1957.
14. Migeon, C. J., Wall, P. E., and Bertrand, J.: *J. Clin. Invest.* 38: 619, 1959.
15. Cohn, E. J., Gurd, F. R. N., Surgenor, D. M., Barnes, B. A., Brown, R. K., Derouaux, G., Gillespie, J. M., Kahnt, F. W., Lever, W. F., Liu, C. H., Mittelman, D., Mouton, R. F., Schmid, K., and Uroma, E.: *J. Am. Chem. Soc.* 72: 465, 1950.
16. Levitz, M., Condon, G. P., Money, W. L., and Dancis, J.: *J. Biol. Chem.* 235: 973, 1960.
17. Levitz, M., Condon, G. P., and Dancis, J.: *Endocrinology* 58: 376, 1956.
18. Zaffaroni, A., and Burton, R. B.: *J. Biol. Chem.* 193: 749, 1951.
19. Barton, G. M., Evans, R. S., and Gardner, J. A. F.: *Nature (Lond.)* 170: 249, 1952.
20. Brown, J. B.: *J. Obst. & Gynaec. Brit. Emp.* 66: 795, 1959.

Discussion

DR. HOWARD W. JONES, JR., Baltimore, Maryland. Although the urinary and biliary metabolites of the physiologically occurring estrone have been investigated by Beer and Gallagher, Sandberg and Slaunwhite, and Migeon, Wall, and Bertrand, Drs. Twombly and Levitz, because of their clinical orientation, have been stimulated to study the metabolites of the therapeutically important compound—estrone sulfate. I hope I may be permitted to recapitulate some of the important findings of this basic investigation in order to keep them clearly in mind:

After the administration of a single dose of radiosodium estrone sulfate by mouth, approximately 55 per cent of the radioactivity and, therefore, presumably 55 per cent of the steroid nucleus had been excreted in the urine after 48 hours. During the first 3½ hours of excretion, 56 per cent of the excreted radioactivity was already converted to a glucuronide and only 6.5 per cent had remained as sulfate. The remaining 27 per cent of excreted radioactivity was not accounted for in the data. During the interval from 3½ to 24 hours after ingestion of the radioactive substance, the glucuronide conjugation had risen to 86 per cent of the total and the sulfate had fallen to 4 per cent. This represents a rate of excretion about three times that of estrone but with similar partitioning, thus showing that, in so far as glucuronide and sulfate conjugates are concerned, the estrone sulfates

seem to be behaving very nearly as if estrone itself had been administered.

When the glucuronide fraction was partitioned by paper chromatography, the authors report the finding of estrone, estradiol-17β, estriol, 16-epiestriol, and ring-D ketols, not further specified. Most of these compounds have been identified by other workers after the administration of estrone. At this point I would like to raise with Dr. Twombly the question of whether the identity of these metabolites in his work has been established in a completely satisfactory manner. The evidence presented is that they move for the same distance on the test filter paper strip as the suspected pure compounds do on a control strip. I should like to ask if there are not other compounds with very similar R_f values which may be and often are confused with each other unless more meticulous identification is carried out. I am told by Dr. Claude Migeon, an associate with whom I have had the privilege of reviewing this paper, that the absolute identification of compounds on a filter paper strip is an exceedingly difficult and troublesome procedure and that authors lacking more convincing proof are sometimes content to say simply that the compound in question moves on the filter paper for a distance similar to that of the suspected compound.

Drs. Twombly and Levitz have nicely confirmed for estrone sulfate the hepatobiliary-

enteric circulation previously demonstrated for estrone by showing that the combined biliary and urinary excretion of radioactivity is greatly in excess of that from the urine alone within a 48 hour period.

The final important and stimulating finding is the demonstration that 5 minutes after injection the plasma contains only a very small fraction (15 per cent) of the injected dose of radioactivity. This rapid disappearance of estrogen from the plasma has also been previously demonstrated for estrone. The total excretion in the urine at the end of 48 hours following intravenous injection of estrone sulfate differs little from that observed after administration by mouth. The questions naturally arise as to what happens to the injected radioactivity and the significance of the disappearance on the tissue or intracellular mechanism of estrogen action.

There is only the slightest evidence in the human, and none at all with a radioactive tracer in the steroid nucleus, for the tissue localization and concentration of estrogens, so that much work needs to be done with the tools and techniques which Dr. Twombly holds in his hands. Such evidence as there is indicates that there may be an important concentration of estrogen in specific tissues—breast cancer and cervical epithelium, but interestingly enough not endometrium. When he completes the investigations which he plans, he should be able to tell us whether estrogens do, in fact, act by appreciably concentrating in specific tissues the target organs for example, or whether they act by simply flipping the enzymatic switch as they pass through the cell to their fate, already studied so carefully by Drs. Twombly and Levitz.

Until this next chapter is available, we must rest content in the knowledge that, if the specific identity of the metabolites may be more firmly established, estrone sulfate seems to be

quickly converted in the human into a state which allows its metabolism to be carried forward in a manner entirely comparable to that of the naturally occurring estrone. This is reassuring information for the physiologically minded clinician to take into his examining room.

DR. TWOMBLY (Closing). I am well aware of the justice of Dr. Migeon's criticism of our saying that we have identified these compounds by their R_f values. I am reminded of this by Dr. Levitz who always says I must not call these compounds estrone, estradiol, estriol, etc. All we can say is that the substances we find in the urine behave like authentic samples of these steroids. I think this is a great deal like going hunting for deer and having a buck jump out of the bushes and then having somebody say, "Are you sure that isn't an antelope escaped from the zoo?" No, of course you aren't sure, but you assume it is not because the antelope would not be likely to be there. From my clinical point of view, these probably are what we think they are.

Table I in the text shows what we did with sodium estrone sulfate C^{14} given intravenously. Urinary assays from 3 to 30 minutes after injection, at which time 2.4 per cent of the dose appears in the urine, show 96 per cent is sulfate and 2 per cent is glucuronide. As more of the injected dose appears in the urine and the amount of sulfate decreases, the glucuronide increases. Dr. Levitz is willing to say that he thinks the urinary excretion of labeled steroids increases as the percentage of glucuronide in the blood rises. There is a parallelism in the percentage of glucuronide present in the blood and the radioactivity excreted in the urine, and this points to the possibility that glucuronide goes through the kidney more readily than does sulfate.

An experiment in the use of radioactive gold for cervical cancer

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WE STARTED an experiment in the use of radioactive gold for the treatment of cancer of the cervix in 1954. The superior results reported by others¹ who used this form of irradiation suggested to us that further studies should be performed to establish the value of radioactive gold in the treatment of cancer of the cervix. Previous reported experiences in the use of this form of treatment, while appearing to support a thesis that radioactive gold was as efficient as, if not superior to, traditional irradiation therapy, were not wholly convincing to us. The reasons for this were that in previous reports the patients were selected to some degree and those treating the patients did not have exact knowledge of the anatomical extent of the disease before treatment. This is a report of an experiment designed and performed to test the efficiency of radioactive colloidal gold in the treatment of cervical cancer.

Methods and materials

The subjects were patients admitted consecutively to the Colorado General Hospi-

tal and Denver General Hospital with invasive cancer of the cervix. They were unselected for the study, except for one patient (one patient in the gold series was not included in the tabulated results since laparotomy was not performed because of medical contraindications). Each patient was classified according to the clinical stage of the disease according to the International Classification.² A pelvic laparotomy was performed on each patient for the purpose of establishing the anatomical extent of disease. The pelvic lymph nodes were removed and biopsy specimens of the parametrial tissue were obtained in the 44 unselected patients of the study. Alternate patients had 150 mc. of radioactive colloidal gold injected directly into the parametrial tissues at the time of laparotomy. Sixty to eighty milliliters of colloidal gold solution in saline was injected into the parametrial tissues. The injections were done under direct vision through the abdominal incision. The other patients were treated with intracavitary radium immediately after the closure of the abdomen. One half of the radium dosage was given at the first application; the remainder was administered 7 to 10 days later. The patients receiving colloidal gold were returned to their rooms after recovery from the anesthesia. Approximately one week after the exploratory operation, the gold series patients were given the first radium application. The second application of radium was given 7 to 10 days later. The gold-

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Table I. Summary of complications and results in 44 patients

<i>Hospital No.</i>	<i>Onset of treatment</i>	<i>Clinical stage</i>	<i>Ana- tomical stage</i>	<i>Significant operative and microscopic findings</i>	<i>Complications of treatment</i>	<i>Results</i>	
61917	X-ray	3/54	III	IV	Positive lymph nodes	None	Died. Extrapelvic metastasis
60620	Radiogold	1/54	III	II	Parametrial infection and metastasis	Rectal stricture, proctitis, and colostomy	Died. Local recurrence
63655	X-ray	5/54	II	II	None	None	Alive
11309	Radiogold	7/54	I	I	None	Severe proctitis	Died. Local recurrence
66342	X-ray	8/54	II	II	Endometriosis and salpingitis	None	Died. Extrapelvic metastasis
66619	Radiogold	9/54	II	II	None	Severe proctitis	Died. Local recurrence
66641	X-ray	9/54	I	I	None	None	Alive
67041	Radiogold	9/54	II	IV	Positive lymph nodes	None	Died. Local recurrence
67398	X-ray	9/54	II	IV	None	None	Died. Local recurrence
67719	Radiogold	10/54	III	IV	Salpingitis	Compound fistula	Died. Local recurrence
49289	X-ray	10/54	I	I	None	None	Alive
67828	Radiogold	10/54	II	II	None	Compound fistula	Alive
70345	X-ray	1/55	I	IV	Ovarian cyst and positive nodes	None	Alive
70555	Radiogold	2/55	I	I	None	Severe proctitis	Died. Extrapelvic metastasis
71226	X-ray	2/55	I	I	None	Proctitis; compound fistula	Died. Local recurrence
73177	Radiogold	4/55	II	IV	Positive nodes	Proctitis and stricture	Died. Local recurrence
73386	X-ray	5/55	III	IV	Positive nodes	Proctitis	Died. Local recurrence
74986	X-ray	7/55	III	II	Ovarian cyst and salpingitis	Severe proctitis	Died. Local recurrence
76991	Radiogold	9/55	III	II	Salpingitis	Severe proctitis	Died. Local recurrence
76881	X-ray	9/55	II	II	Appendicitis	None	Died. Local recurrence
77166	Radiogold	9/55	II	II	None	Obstruction and wound dehiscence	Died. Operative complications
77690	X-ray	10/55	II	IV	Positive nodes	None	Died. Local recurrence
77761	Radiogold	11/55	I	I	None	Severe proctitis	Died. Local recurrence
78745	X-ray	11/55	I	I	Endometriosis	Severe proctitis and cystitis; colostomy	Alive
79365	Radiogold	12/55	I	I	None	Intestinal obstruction	Died. Extrapelvic metastasis
79450	X-ray	12/55	II	IV	Positive nodes	None	Died. Pelvic recurrence
77238	Radiogold	2/56	II	II	Pelvic inflammation	Intestinal obstruction	Died. Local recurrence
289720	X-ray	1/54	I	I	Bilateral salpingitis	None	Alive
299626	Radiogold	2/54	III	III	Salpingitis, ovarian cyst	Proctitis; compound fistula	Died. Extrapelvic metastasis
295744	X-ray	2/54	I	I	None	None	Alive

Table I—Cont'd

<i>Hospital No.</i>	<i>Onset of treatment</i>	<i>Clinical stage</i>	<i>Ana- tomical stage</i>	<i>Significant operative and microscopic findings</i>	<i>Complications of treatment</i>	<i>Results</i>	
373	Radiogold	5/54	I	I	None	None	Alive
5317	X-ray	9/54	IV	IV	Positive nodes	None	Died. Local re- currence
8739	Radiogold	10/54	III	III	None	Severe proctitis and cystitis	Died. Local re- currence
9554	X-ray	11/54	III	III	None	None	Alive
17274	Radiogold	4/55	III	IV	Positive nodes	Proctitis and rectal stenosis	Died. Local re- currence
52	X-ray	5/55	I	IV	Positive nodes	None	Died. Extrapelvic metastasis
22394	Radiogold	6/55	III	II	Pelvic infection and induration	Compound fistula	Died. Local re- currence
4699	X-ray	6/55	I	I	None	None	Alive
17707	Radiogold	6/55	I	I	None	Proctitis and rectal stenosis	Died. Extrapelvic metastasis
28486	X-ray	8/55	IV	IV	Positive nodes	None	Died. Local re- currence
12047	Radiogold	9/55	I	I	None	None	Alive
20119	X-ray	9/55	I	I	None	None	Alive
39345	Radiogold	10/55	III	III	None	None	Alive
56939	X-ray	2/56	II	II	None	Severe proctitis, colostomy	Alive

treated group received radium but no external irradiation therapy, whereas alternate patients received radium and our usual external x-ray therapy.

The 44 patients fell into the following clinical stages according to the International Classification for clinical staging of cancer of the cervix: Stage I, 17; Stage II, 13; Stage III, 12; Stage IV, 2.

Results

The exploratory laparotomy and biopsies performed for the purpose of establishing the extent of the disease revealed the following:

Two of the 17 patients with Stage I disease had positive pelvic lymph nodes found at operation, making 12 per cent difference between the clinical and anatomical extent of the disease in Stage I.

Five of the 13 patients with Stage II cancer had lymph nodes that contained cancer, and one of them had extensive parametrial involvement not appreciated before anatomical staging. In Stage II, the

error was 39 per cent, illustrating our tendency to underestimate the extent of disease through clinical methods.

Twelve patients with clinical Stage III cancer showed errors in preoperative staging of the disease. Three had cancer in the pelvic lymph nodes and one had extension of tumor to the bladder wall that was unrecognized through the cystoscope. Four other Stage III patients had parametrial infections which were erroneously interpreted as cancer. Thus, one third of Stage III patients were anatomical Stage II, while another one third were anatomical Stage IV. The total staging error for Stage III patients was 67 per cent. There were no errors in classification of Stage IV patients. The limitations of clinical staging in judging the anatomical extent of disease have been reported.³

A clinical summary of each of the 44 patients is listed in Table I.

The anatomical extent of disease after laparotomy and biopsy was: Stage I, 15; Stage II, 12; Stage III, 4; Stage IV, 13.

The selection of patients on an every

other hospital admission basis divided the two groups into the following clinical stages:

Radium and x-ray. Stage I, 10; Stage II, 7; Stage III, 4; Stage IV, 2; total 23.

Gold and radium. Stage I, 7; Stage II, 6; Stage III, 8; Stage IV, 0; total, 21.

The two groups were divided after laparotomy and biopsy into the following anatomical stages:

Radium and x-ray. Stage I, 8; Stage II, 5; Stage III, 1; Stage IV, 9; total, 23.

Gold and radium. Stage I, 7; Stage II, 7; Stage III, 3; Stage IV, 4; total 21.

Morbidity and mortality. There was no significant immediate morbidity in the radium and x-ray treated group. Immediate major complications occurred in 14 per cent of the patients treated with gold. These complications were small bowel obstruction in 2 patients and a wound evisceration which caused death in one.

Delayed complications of radium and x-ray treatment occurred in 5 patients (22 per cent). Fourteen of the 21 patients of the gold-treated group had severe delayed complications of treatment. The complications for each group appear in Table II.

Fourteen of the 21 patients in the gold-treated group developed irradiation proctitis 6 weeks to 3 months after treatment. Four of the patients in the gold series developed a vesicovaginal or rectovaginal fistula. The patients of the radium and x-ray series developed irradiation proctitis in five instances, one of which resulted in a rectovaginal fistula.

Table II. Delayed complications of treatment

	<i>Radium and x-ray (23 patients)</i>	<i>Gold and radium (21 patients)</i>
<i>Intestinal</i>		
Severe proctitis	4	9
Obstruction		1
Fistulas (rectal)	1	3
<i>Genitourinary</i>		
Fistulas		1
Total	5 (22%)	14* (67%)

*All had irradiation proctitis.

Table III. Four- to six-year survival of patients

	<i>Radium and x-ray (23 patients)</i>		<i>Gold and radium (21 patients)</i>	
	<i>Clinical</i>	<i>Anatomical</i>	<i>Clinical</i>	<i>Anatomical</i>
Stage I	8	7	2	2
Stage II	2	2	1	1
Stage III	1	1	1	1
Stage IV	0	1	0	0
Total	11 (48% survival rate)	11	4 (19% survival rate)	4

All 44 patients of this study have been followed from 4 to 6 years. Forty-eight per cent (11) of the 23 radium and x-ray treated patients are alive and well at this time. Nineteen per cent (4) of the patients who were treated with gold and radium are alive and well 4 to 6 years later. The patients with cancer of the cervix treated by the two different methods who are still alive are listed in Table III.

Comments

This is a small series of patients to study and draw conclusions from concerning the benefits of a particular form of treatment. Even though the study is limited by numbers of patients, we do wish to emphasize that this was a study on alternate patients of histologically proved invasive cancer of the cervix, and that the patients were unselected. The second aspect of this study that is important, we believe, is that the anatomical extent of the disease was established as exactly as possible by laparotomy and pelvic tissue biopsy before treatment was given. The anatomical extent of the disease did not cause us to change the form of treatment for any patient.

The study continued for only 2 years because the serious delayed complications of gold therapy caused us to discontinue the experiment.

The alternate patient study method permitted the patients to fall into groups of approximately equal severity of specific dis-

ease process. To illustrate, the radium and x-ray group had 13 patients in anatomical Stages I and II, while the gold and radium group had 14 in anatomical Stages I and II.

It may not be correct to ascribe death of a patient with cancer of the cervix to the method of treatment. In order to avoid this, we have analyzed the causes of death among the 17 patients treated with gold and radium and the 12 patients treated with x-ray and radium who died. In the gold and radium group, 60 per cent (12) of the patients died with pelvic recurrence of the disease. Five others died of either distant metastasis or complications of treatment. For comparison, 35 per cent (9) of the radium and x-ray group died with pelvic recurrence. Three of the radium and x-ray group died with distant metastasis. This suggests that the gold treatment was not effective in the treatment of pelvic cancer.

Considering the high morbidity and the low cure rate found in the patients treated with injected colloidal radioactive gold by our method, supplemented by intracavitary radium, we have discontinued the use of radioactive gold in the treatment of cervical cancer. In our hands the traditional method of irradiation therapy (radium and x-ray) is much superior.

We are unable to explain our poor clinical results with radioactive gold when compared to those of Allen, Sherman, and Arneson,⁴ and Veldhuis, Swinehart, and Preuss.⁵ At first we thought that the preliminary operation done for diagnostic purposes might be prejudicing our results. This, however, seems not true since the preliminary operation in the radium and x-ray group seemed unimportant in terms of final results. The technique we used in injecting the radioactive gold by the intra-abdominal approach following the biopsy of the lymphatics perhaps caused some disruption of the tissue planes

and caused pooling of gold, making it unavailable for lymphatic permeation.

Conclusions

1. Injection of parametrial tissues with colloidal radioactive gold in solution was associated with a 67 per cent rate of delayed major complications. This was three times the complication rate in a control group of patients treated with radium and x-ray.

2. Only 19 per cent of all patients with invasive cancer of the cervix treated with radioactive gold and radium are alive and well 4 to 6 years later. Forty-eight per cent of 23 control patients with a comparable extent of disease treated with traditional radium and x-ray methods are alive and well 4 to 6 years later.

3. We do not recommend that radioactive gold be used in the treatment of cancer of the cervix, and we have discontinued its use for this purpose in our clinic. It appears to be less effective as a supplement to radium in the treatment of cancer of the cervix than external deep x-ray therapy.

Summary

Forty-four unselected patients were treated for invasive cervical carcinoma. Alternate patients were treated with radioactive gold and radium while the other patients of the series received traditional radium and x-ray treatment. The errors inherent in clinical staging methods are presented. The results of treatment in the two groups of patients are analyzed. Patients treated with radioactive gold suffered a high percentage of immediate and delayed complications of treatment when compared to the group treated by traditional irradiation methods. The 4 to 6 year survival rate in the gold-treated group was but 19 per cent, as compared to 48 per cent 4 to 6 year survival rate in the group treated with radium and x-ray.

REFERENCES

1. Allen, Willard M., Sherman, Alfred I., and Arneson, A. Norman: *AM. J. OBST. & GYNEC.* 68: 1433, 1954.
2. Heyman, J.: *Acta obst. et gynec. scandinav.* 28: 175, 1949.
3. Isbell, N. Paul, and Dean, Robert E.: *Obst. & Gynec.* 10: 6, 1957.

4. Allen, Willard M., Sherman, Alfred I., and Arneson, A. Norman: *AM. J. OBST. & GYNEC.* 70: 786, 1955.
5. Beldhuis, Andrew H., Swinehart, L. A., and Preuss, L. E.: *Henry Ford Hosp. Bull.* 4-6: 144, 1956-58.

Discussion

DR. JAMES F. NOLAN, Los Angeles, California. Dr Taylor's conclusion that parametrial infiltration with radiogold plus intracavitary radium is a method inferior to external radiotherapy plus intracavitary radium, in cervical cancer, seems highly justified within the confines of his experiment. However, the desire to assess the advancement of the disease as accurately as possible so that a comparison of the results of the two treatment methods would be realistic may have imposed some limitation upon the conclusions.

The experiment may not, therefore, be completely applicable to test the comparative efficacy of the treatment methods as they are applied under the usual conditions. The preliminary parametrial and nodal biopsy procedures may have exerted a deleterious effect upon the subsequent radiotherapeutic procedures. The preliminary operation may also be more deleterious to the results of the interstitial infiltration than to the external radiation technique.

From a theoretical standpoint the surgical disruption of the tumor bed may have introduced a factor disadvantageous to radiotherapy. Throughout the years there has been a desire on the part of radiotherapists to deliver a uniform dosage pattern to the areas of potential involvement by cervical cancer. When parametrial infiltration was first described, an objection to it was raised upon the grounds of possible spotty dosage distribution. Preliminary reports on results of treatment by parametrial infiltration seemed to obviate this theoretical objection, but in the clinical experiment described here the addition of the surgical trauma to the subsequent trauma of radiation therapy may have been a factor in the ultimate outcome.

The surgical disruption of tissue planes, necessary in the removal of pelvic lymph nodes and the dissection of the parametrium, interferes with the distribution of the injected material. In monkey experiments involving direct injection of the parametrium we found that the leaves of the broad ligament had to be intact for the best distribution of the material. Since it is injected under some pressure there

is a distention of the tissue, and leakage or pooling may occur if the anatomic planes are interfered with. The handicap imposed by such surgical distortion weigh against the radiogold-treated patients rather than the external radiation group of the reported study.

It is difficult to explore the supposition that the preliminary operation may have been deleterious. However, an attempt has been made with use of the results of our own experience. The apparent recovery rate for the 5 year period of 1949 to 1953 for the patients with cancer of the cervix treated at the Los Angeles Tumor Institute has been found to be 74, 53, 28.2, and 0 per cent, respectively, for Stages I to IV. These results compare favorably with the collected statistics in *The Annual Report on the Results of Treatment of Uterine Cancer* during the same time interval, which are 70.0, 48.6, 27.3, and 6.7 per cent, respectively, for the same stages. If we should assume that our results would continue to be "standard" we can use the experience gained during the same time period as Dr. Taylor's experiment for comparison.

During the years 1954 and 1955 a total of 55 patients with all stages of the disease were treated by means of cobalt⁶⁰ teletherapy plus intracavitary or interstitial radium. Of these, 42 (or 76 per cent) at present survive without evidence of disease. If this group be adjusted to Dr. Taylor's according to stages on the basis of clinical evaluation (our patients were not subjected to surgical exploration) we find that 66 per cent presently survive. This figure is higher than the 48 per cent surviving in his conventionally treated group, and the difference is statistically significant at the 5 per cent level. It is considerably higher than the 19 per cent surviving in his radiogold plus radium group.

Such a numerical comparison, even though a superficial one, again points to the fact that the preliminary operation may well have led to poorer results from both techniques but that the results of treatment in the radiogold group may have suffered disproportionately more. If this supposition be true, one can hardly extrapolate the comparative results reported here to

groups of patients who might be treated by the two methods without the preliminary parametrial biopsies.

Despite this one objection, Dr. Taylor's study casts some doubt upon the value of the parametrial gold technique. Although the preliminary reports concerning the method have been most enthusiastic it would seem advisable to await the results of further comparative studies, such as that presented here, before the more conventional external radiation techniques be abandoned in favor of the interstitial isotope therapy.

DR. C. PAUL HODGKINSON, Detroit, Michigan. In the gold-treated group the authors observed a high percentage of major complications and a sharp reduction of salvage. Their poor results were in conflict with favorable reports by others. The question arises if alterations in technique, incidental to accomplishing the restrictions imposed by the scientific design of the experimental study, contributed to the high complication and low death rates.

When first introduced, the use of radioactive colloidal gold, given by transvaginal injection into the parametrium, was appealing. The principle of assailing tumor and cancer-bearing lymphatics with high energy beta radiation, from within rather than from without, was a new modality of cancer therapy with interesting, but unproved, potentialities.

It was quickly apparent that prompt dispersion of the injection bolus was the key to success. If complications from local tissue necrosis were to be prevented, pooling and delayed absorption must not occur. Also, because the penetrating effect of beta radiation from Au^{198} is less than 5 mm. and because the half life is 2.69 days, the cancerocidal effect is directly proportional to the speed with which it gains access to the regional lymphatics.

In an experimental study with rabbits, Veldhuis, Swinehart, Preuss, and Hodgkinson observed the means and rate of transport of interstitially placed radioactive colloidal gold. In general, our results were the same as those reported by others. They showed that the injection bolus was quickly removed from the site of injection. However, after 7 days, local tissue necrosis was evident which went on to heal by fibrous tissue replacement. It was also shown that mobilization occurred mainly through the lymphatics. The ratio of lymphatic to homogenous

spread was in the order of 100 to 1. The effects on the lymph nodes were impressive. At 7 days microscopic examination showed the colloid to have been eagerly ingested by macrophages; the lymph nodes were mildly hyperplastic and intensely infiltrated by plasma cells. By 14 days the nodes were essentially depleted of lymphocytes, leaving evident the fibrous tissue architecture. By the twenty-eighth day, the nodes were again filled with lymphocytes and endothelial cells.

This study gave a fairly complete idea of the reaction of the normal lymph node in the intact animal to Au^{198} . It did not answer the question as to what occurs to transport efficiency when the lymph node is filled with tumor or when it has been removed by operation.

Between 1954 and 1957, in Henry Ford Hospital, 22 patients received treatment for carcinoma of the cervix according to the technique used by Allen, Sherman, and Arneson. Radioactive colloidal gold was injected transvaginally into each parametrium in total doses which varied from 70 to 150 mc. In addition, all were treated with intracavitary radium, the average dose being 5,500 r. Later, radical hysterectomy was performed on 16 patients.

According to the International Classification the extent of the disease was judged as follows: Stage I, 6; Stage II, 12; Stage III, 2; and Stage IV, 2.

Eight of the patients are dead: 6 died of malignancy, 2 died from complications of treatment. According to the stage of malignancy, deaths occurred as follows: Stage I, 0; Stage II, 5; Stage III, 1; and Stage IV, 2. The 3 year salvage rate was 64 per cent.

The complication rate was high. Severe sciatica persisted in 14 patients. Compound vesicorectovaginal fistulas developed in 2 patients, both of whom are dead. Another patient, 6 months after treatment, developed small bowel obstruction from a fibrous ring of radiation reaction, colloidal gold being observed in the excised segment of bowel. Many patients complained of sensory bladder disturbances and 4 patients became incontinent. Stricture of the left ureter was observed once. Proctitis was noted twice.

From a comparison of results, it appeared unlikely that the high complication rate reported by Taylor, Isbell, and Dean occurred as the result of pooling or delayed absorption. It is difficult to account for the difference in sal-

vage rates. While our 3 year salvage rate is in an acceptable range, we too discontinued using Au¹⁹⁸ for cancer of the cervix because of the high incidence of major complication.

DR. TAYLOR (Closing). Dr. Nolan's suggestion about the technique's being the possible cause of the prejudiced results to gold is a legitimate

one. I know of no way to prove or disprove that theory at this time.

It was interesting to hear Dr. Hodgkinson report corroboration of our experience to the effect that gold is not only inefficient but damaging. As much as we would like to see a better and more effective treatment introduced for carcinoma of the cervix, I cannot help but think that gold is not an advance to be introduced into our present methods of treatment.

Sodium cyanide as a cancer chemotherapeutic agent

Laboratory and clinical studies

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THE treatment of genital malignancies has undergone major revision during the past half century. The unsatisfactory results at the turn of the century with surgery and cautery were gradually improved by the application of internal and external radiation, and, with its standardization in the past two decades, this modality has provided most satisfactory results for selected cases. In the forties and fifties there was a revival of the surgical effort and after extensive exploration, the advantages and limitations of this form of therapy have likewise been delineated. By the middle of this century, therefore, gynecologists recognized radiation and surgery as complementary rather than competitive forms of therapy for the earliest stages of the disease.

It became obvious that cures of carcinoma of the cervix could be obtained by either type of therapy, provided the lesion was confined to the epithelium or minute stromal invasion. With the rapidly developing reliability of the cytologic screening methods of

Papanicolaou, our attention has been directed to the finding and selecting of patients most amenable to these very satisfactory forms of therapy. The combination of routine gynecologic examination and cytologic screening with the proper selection of patients for the two standard methods of therapy has exhibited most satisfactory clinical results.

However, from two thirds to three fourths of the patients seen were in unfavorable clinical categories, primarily because women were not submitting themselves to gynecologic and cytologic studies. As a consequence, there is a large number of patients with gynecologic cancer who present an unfavorable clinical picture for any of the present therapy programs.

The second half of the century has seen a revival of the concept of "cancer poisons" which had been explored intermittently much earlier. These efforts are an extension of such activities as the use of Fowler's solution, colchicine, and benzene in the treatment of leukemia. Cyanide, the subject of this report, had its chemotherapeutic beginnings in 1927¹ and was further explored in the thirties, but pursuit of this modality was abandoned because of its high toxicity and the rapidly improving results from radiation therapy at that time.

Recent basic research in the field of chemo-

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May 30-June 1, 1960.*

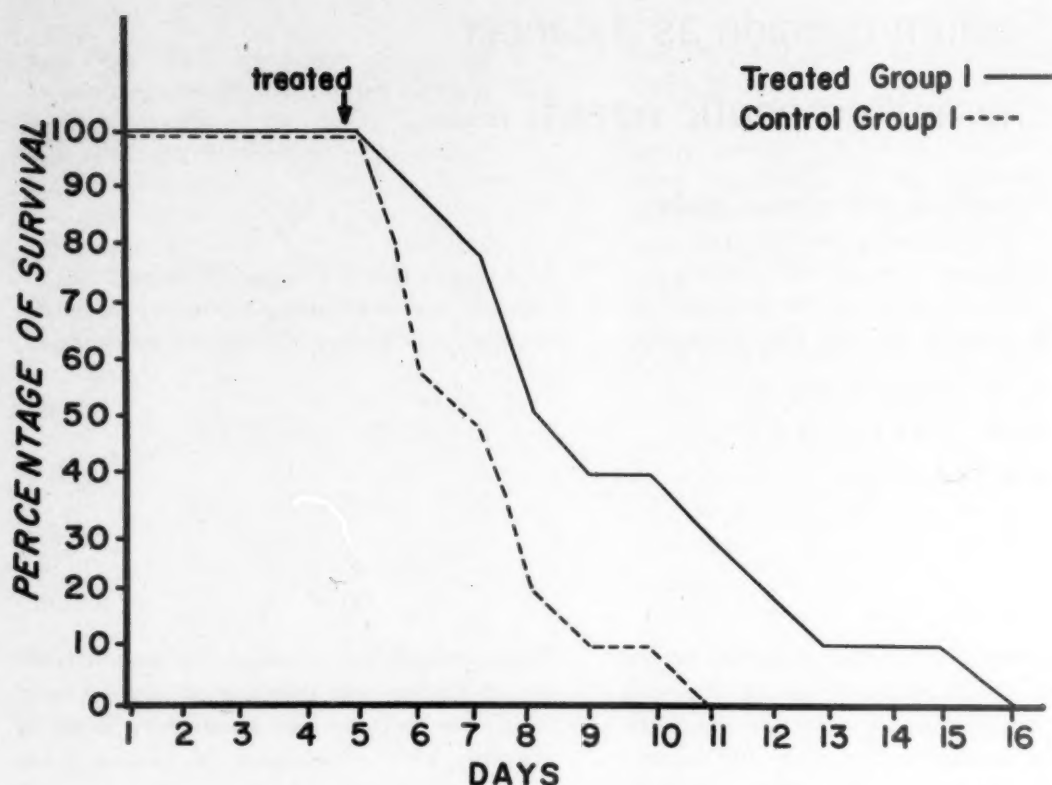


Fig. 1. Survival curves showing comparison between control Ehrlich's ascites mice and animals treated with 0.75 mg. per kilogram cyanide and ether anesthesia (8×10^7 cell inoculation).

therapy in cancer has concerned itself with several areas of cancer cell activity. Some of these have centered about the increased mitotic activity of cancer cells in contrast to normal tissue. Radiation is presumed to produce either death of those cells in mitosis or the development of mutants which are incapable of independent survival. The alkylating agents, which are sometimes referred to as radiomimetic agents, probably act in a similar manner by interfering with the nucleic acid stability during mitotic division.

The second approach is in the area of cellular metabolism. Many studies are currently in progress and others are being explored. Some of their effects are on specific metabolic functions such as the synthesis and metabolism of folic acid, purine, and pyrimidine, and others are more general in nature.

Third, there is much study of the immune reactions which may develop in the host toward the several forms of tumor invasion.

An example of this is seen in the localization and eventual destruction of the metastatic tumors from chorioadenoma destruens.

Further, there are the peculiar aspects of the steroid hormones and the trophic support of those tissues and tumors which are linked to the sex steroids, such as uterus, breast, and prostate.

Finally, there are certain chemical agents that have an effect on the several enzyme systems within the cell, such as oxidative phosphorylation through action on the cytochrome oxidase.

Most basic research in cancer has concerned itself primarily with those deviations in which the malignant tissue has shown an excess or hyperactivity as compared with normal tissue. Recently there have been studies along the philosophical line that it might be profitable to explore those areas in which the cancer cells show a modifiable deficiency. Warburg's studies² have suggested

that tumor tissues have a deficiency of oxidative phosphorylation. He contends that this is the result of an irreversible mutation in the enzymatic capacity of the malignant cells and that oxidative metabolism may approach an irreducible minimum. Chance and Hess³ have shown that the addition of glucose to certain tumors causes a rapid acceleration of tissue respiration. The observations of Quastel and Rickis⁴ have shown that respiration and phosphorylation are tightly coupled in the malignant cells, and they suggested that the inhibitory action of certain chemotherapeutic substances on the tumor tissue, particularly the cytochrome oxidase, might provide an interesting field for study of cancer therapy.

As indicated previously, cyanide had been explored as a tumoricidal agent by Karczag¹ in 1927, by Maxwell and Bischoff⁵ in 1933, and by Perry⁶ in 1935, all of whom found that cyanide seemed to have a differential inhibitory effect upon tumor tissue, but the margin of safety appeared so low that clinical

usefulness did not appear to be probable. Galkin⁷ subsequently demonstrated that the acute toxicity of cyanide could be reduced by the concomitant administration of an anesthetic. A review of the literature reveals several interesting uses of this toxic agent for various clinical effects.⁸

Sodium cyanide acts primarily by inhibiting the cytochrome oxidase and would have certain theoretical advantages should it be shown to be an effective cancer chemotherapeutic agent. Because the action of sodium cyanide is almost instantaneous and since normal tissues and cells are capable of recovering from its noxious effects, it could be anticipated that there would be no cumulative effect or latent complications in the bone marrow, the gastrointestinal tract, or the renal apparatus.

During the past several years we have been interested in regional perfusion in chemotherapy, and it seemed feasible to explore the role of this antienzyme, sodium cyanide, in regional perfusion for pelvic malignancy.

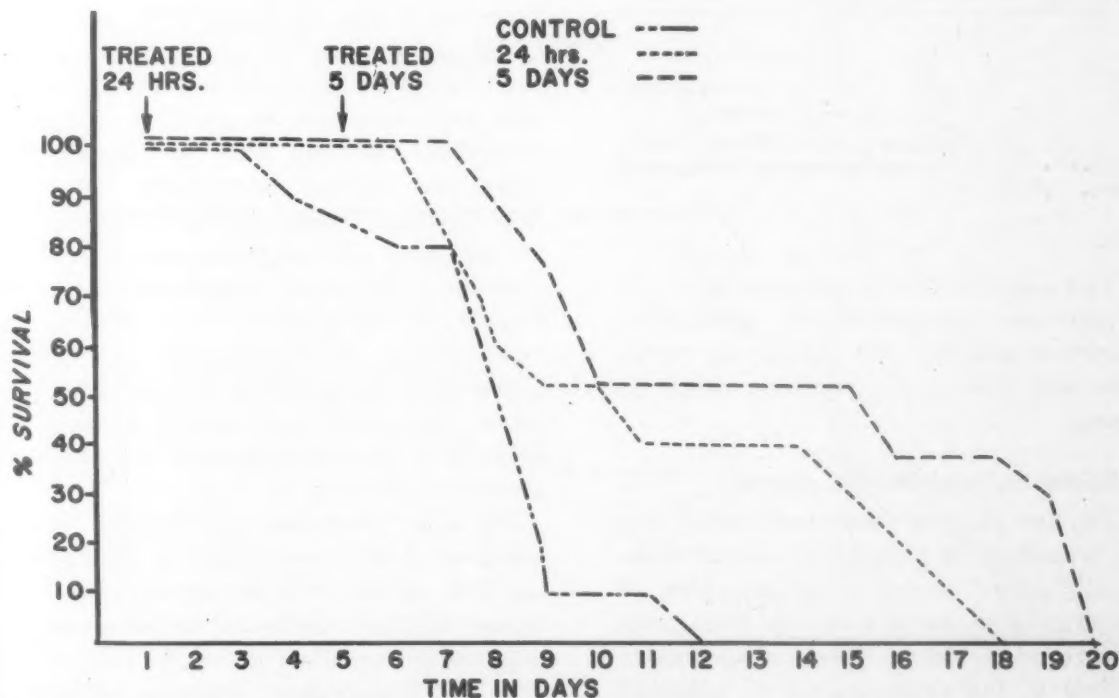


Fig. 2. Survival curves (4×10^6 cell inoculation) showing comparison between control animal survival and that of animals treated at 24 hours and others treated at 5 days post inoculation with 0.75 mg. per kilogram sodium cyanide and ether anesthesia.

Table I. Alteration of survival time in Ehrlich's ascites mice produced by cyanide-anesthesia treatment*

Dosage (mg./Kg.)	Hours post inoculation	Average survival (days)	% Increase in survival
0.75	C. --	8.1	--
	24	9.8	21
	120	10.4	35
1.50	C. --	8.1	--
	24	12.7	57
	48	13.8	70
	120	11.1	37
	24-48-120	12.8	58
	C. --	9.9	--
2.0	48-72	16.6	70
	C. --	8.0	--
	48	12.8	60

*Male Swiss mice inoculated intraperitoneally with Ehrlich's ascites tumor and subsequently with cyanide under ether anesthesia. Each experimental group utilized units of 10 mice for each procedure and control. C = control.

Table II. Alteration of survival time in Sarcoma 180 in mice produced by cyanide-anesthesia treatment*

Dosage (mg./Kg.)	Hours post inoculation	Average survival (days)	% Increase in survival
1.5	C. --	11.4	--
	24	16.9	48
	48	18.4	61
	120	15.2	33
	24-72-120	19.3	70

*Experimental circumstances similar to that for ascites tumor, Table I.

This paper reviews these experiences with cyanide on transplanted and spontaneous tumors in animals,⁹ and reports our experience with advanced gynecologic cancer in women.

Studies in experimental animals

The first phase of these studies dealt with the acquisition of experience and knowledge on the several routes of administration of the cyanide-anesthetic mixtures. Swiss mice, mongrel dogs, and rhesus monkeys were utilized in the determination of tolerance, dosage, and mortality from the several routes of administration of the cyanide-anesthetic

mixtures. Both ether and barbiturates were utilized and both intraperitoneal and intravenous injections of cyanide were studied. The animals were observed for a period up to 6 months after several such treatments in order to determine any physiologic or histologic changes. No latent effects could be observed. While considerable variation occurred in the acute toxicity to the cyanide by the several routes of administration, it soon became apparent that from 0.75 to 1.5 mg. per kilogram was the anticipated average tolerance dose in these animals, and that the rate of intravenous administration had to be varied slightly by the toxic response on the part of the animal. Acute toxicity and mortality from cyanide-anesthetic mixtures were uncommon below 3.0 mg. of cyanide per kilogram of body weight.

With this information available it was decided to explore the effectiveness of cyanide-anesthetic mixtures on two transplantable tumors, Ehrlich's ascites and Sarcoma 180 in mice. The details of these studies have been previously reported.⁹

In the study of the Ehrlich's ascites tumors in mice, animals inoculated 8 days previously served as donors. Malignant cells were obtained under light ether anesthesia by aspiration of the peritoneal fluid, and the neoplastic cells were separated by centrifugation and decanting. The cells were resuspended in saline and injected immediately into the study animals. Because of the peculiarity of the problems of transplantation, it seemed desirable to discard all animals that survived because of the possibility of a failure of transplantation. As a consequence, we decided to use the prolongation of survival time between the control and treated animals as evidence of the effectiveness of the cyanide-anesthetic mixtures.

On a few occasions, an extremely large inoculum of cells was utilized but since there was little difference in the survival time, the balance of the studies were carried out with the standard inoculum of 4×10^6 cells.

At the appropriate intervals following inoculation, the mice were placed under ether anesthesia bell jar until they no longer re-

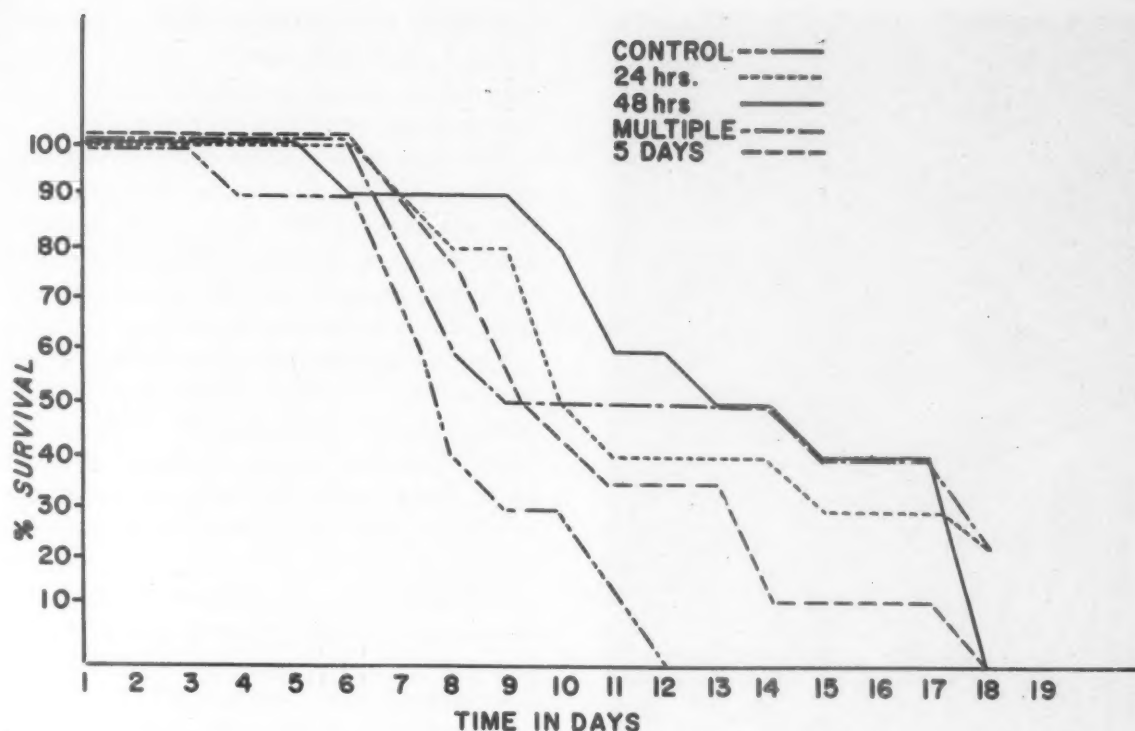


Fig. 3. Survival curves (4×10^6 cell inoculation) comparing survival of control animals with that of animals treated at 24 hours, 48 hours, 5 days and at 1, 3, and 5 days post inoculation with 1.5 mg. per kilogram cyanide and ether anesthesia.

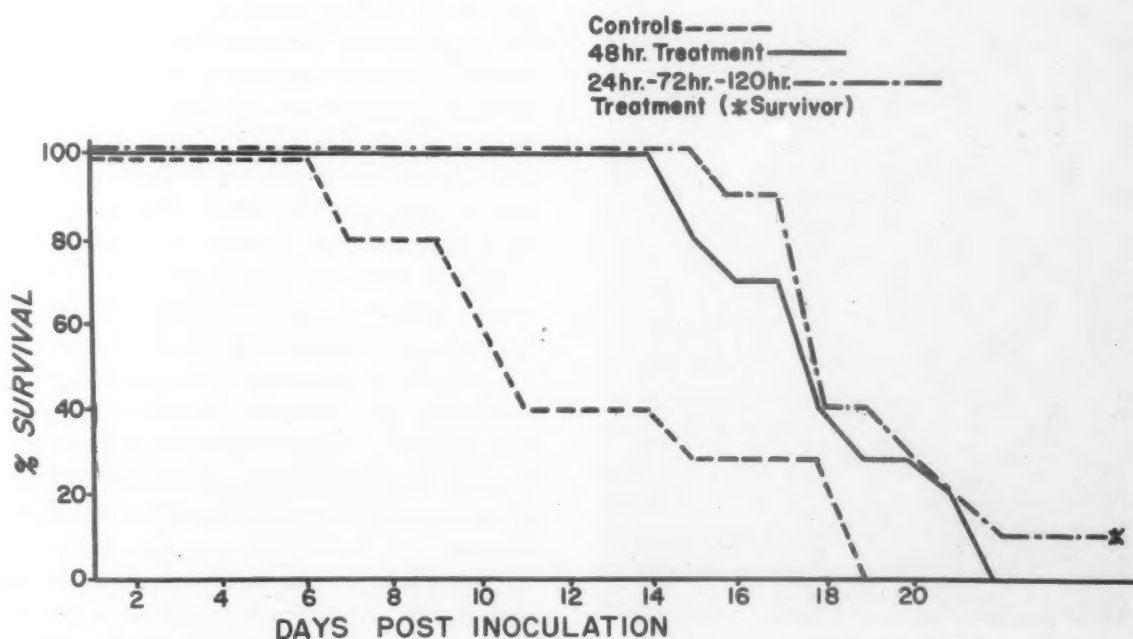


Fig. 4. Comparison of survival time of control and Sarcoma 180 mice treated with 1.5 mg. cyanide per kilogram of ether anesthesia at 48 hours, 24 to 72 hours, and 120 hours post inoculation.

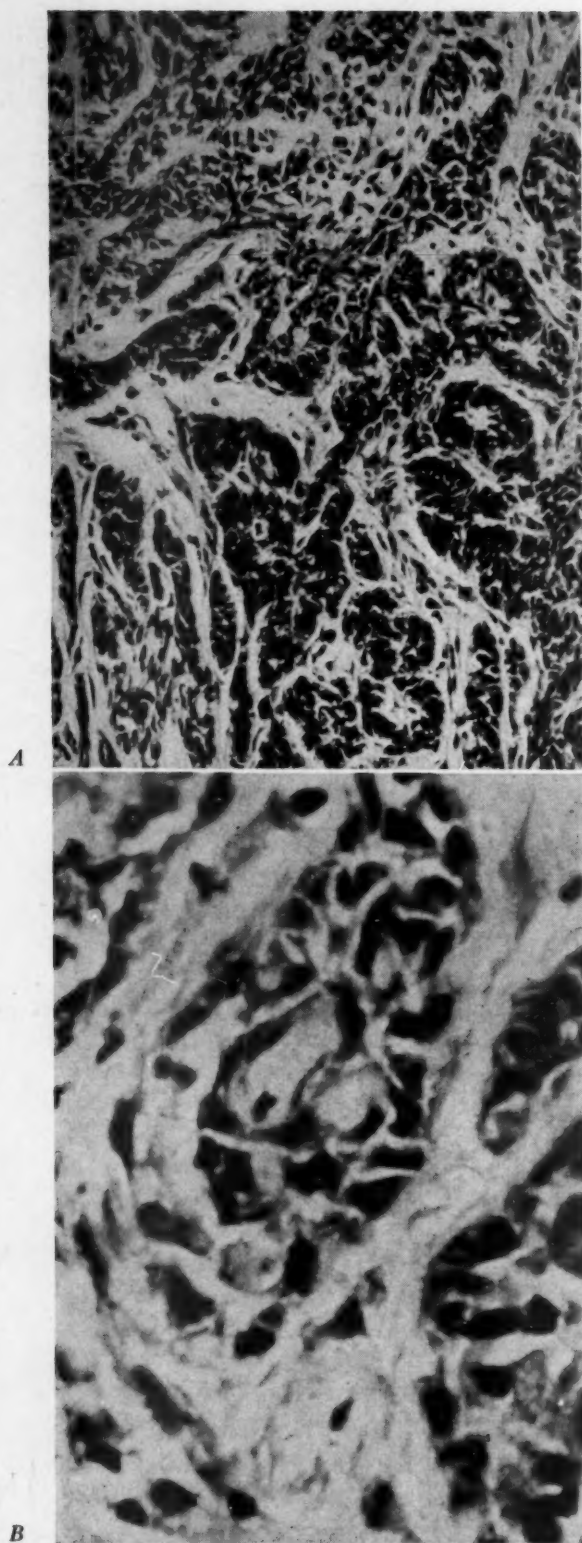


Fig. 5. Biopsy of mammary cancer in dog prior to cyanide-anesthesia treatment. *A*, Low power. *B*, High power.

sponded to painful stimuli. They were then injected intraperitoneally with varying amounts of sodium cyanide and allowed to recover from the ether anesthesia.

The cyanide was given in increasing dosage from 0.75 to 4.0 mg. per kilogram, and the treatments varied from a single treatment 24 hours after inoculation to variable single and repeated inoculations over several days (Table I, Figs. 1, 2, and 3).

The average survival time of the control animals was 8.5 days while that for the animals treated with cyanide varied from 9.8 to 16.6 days or a prolongation of from 15 to 85 per cent. The longest survivals occurred in animals treated early and frequently.

Following the observations on Ehrlich's ascites tumor, similar experiments were carried out with Sarcoma 180. Although the data suggest that Sarcoma 180 is slightly more resistant to cyanide than is the Ehrlich's ascites tumor, similar results were obtained, i.e., that multiple treatments given at 24, 48, and 120 hours after inoculation produced average increase in survival time of approximately 70 per cent (Table II, Fig. 4).

Following these observations, we turned our attention to a study of spontaneous tumors. Through veterinarians and other sources, we were able to accumulate 18 dogs, exhibiting primarily mammary but also a few other spontaneous tumors. Some of the animals showed secondary metastases in addition to the primary tumor. Nembutal was the anesthetic used in the treatment of the dogs and they received from 2 to 4 intravenous perfusions with 1.5 mg. of sodium cyanide per kilogram of body weight.*

Since it was not possible to utilize control studies in the manner employed for the mouse tumors, we elected to utilize histologic changes within the tumor and survival time against the anticipated mortality of these animals.

Consequently, prior to therapy, the animals were lightly anesthetized with Nembutal and a biopsy specimen taken from the tumor or

*This work is awaiting publication.

visible metastasis. Approximately one week later the animals were reanesthetized and a second controlling biopsy specimen was taken at a position remote from the original biopsy site. At this time, the animals received an infusion of sodium cyanide intravenously. The quantity and rate of cyanide administered varied slightly with the clinical response of the animal. In the early studies, the animals were monitored with EEG and ECG tracings, blood pressure recordings, and other clinical observations.

Following treatment, the animals were placed in recovery cages, supported as necessary, and examined frequently for changes in the size and consistency of the primary tumor or metastases. At weekly intervals a subsequent infusion of cyanide was given and a further biopsy specimen taken; this procedure was continued for 2 to 4 episodes.

In several animals large necrotic areas appeared in the softened tumor mass 4 to 6 days after treatment and necessitated reparative excision of necrotic masses in a few animals. The animals were then returned to their owners. Eight animals were followed up for periods of one year and, while no satisfactory statistical data are available for the survival time of these animals, it was the impression of the veterinarians with whom we consulted that this represented a significant prolongation of life in many and an apparent cure in a few.

A study of the tissue obtained through biopsy revealed cellular changes which, while somewhat bizarre and ill-defined, exhibited a consistent pattern. Following the second or third posttreatment biopsy, there was considerable cellular destruction with pyknosis of nuclei, vacuolation of cytoplasm, and aggregates of cellular debris (Figs. 5 and 6). While these changes varied in intensity in all cases, they represented marked changes from findings with the pretreatment biopsy specimens.

It thus appeared that we had established the feasibility of utilizing cyanide-anesthetic mixtures, and the prolongation of survival time in mice and histologic changes in the mammary tumors of dogs offered some evi-

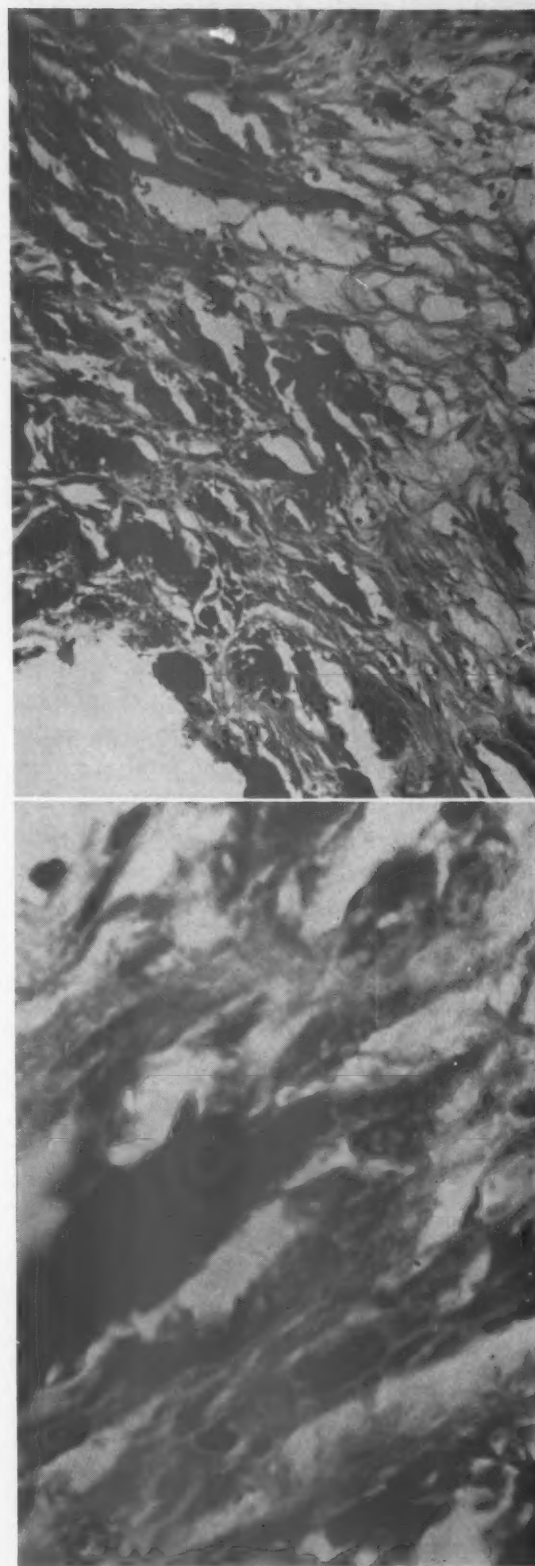


Fig. 6. Biopsy of dog mammary cancer following cyanide-anesthesia treatment. A, Low power. B, High power.

dence that this antienzyme form of chemotherapy for cancer might be clinically useful.

Clinical studies

Patients with extensive carcinoma, primarily of the cervix, were selected for study. Our first efforts were directed at the development of a simplified regional perfusion technique. Since our experience with cyanide had suggested that normal cells and tissues recovered promptly and without cumulative or chronic toxic manifestations, it was not believed necessary to completely isolate the area of perfusion with the complicated extracorporeal circulation systems.

Two techniques were developed for the perfusion of the pelvic viscera. When laparotomy was indicated, the hypogastric arteries were cannulated with or without ligation and the ovarian arteries were clamped, tied, and severed. By radiographic techniques, we were able to visualize rather satisfactorily the extent of the arterial system within the pelvis and the probable distribution of any chemotherapeutic agent thus introduced (Fig. 7). A few studies were done with chromium-tagged red cells and dyes to determine the escape by collateral vascular channels; however, it soon became evident that with the substances under consideration this was not of major importance. Suffice it to say that the majority of the collateral circulation passed through the gluteal to the lumbar and vertebral vessels, and some through the pudendal, epigastric, and femoral vessels. Adequate pelvic concentration of the radiographic dye seemed to indicate a probably satisfactory distribution of the chemotherapeutic agent.

Under other circumstances, we cannulated the femoral artery well down in Hunter's canal and, by passing a polyethylene catheter above the bifurcation of the aorta, we were able to introduce radiographic material and cyanide into the blood stream at this point. By the utilization of pneumatic cuffs about the upper part of the thigh, it was possible to get fairly satisfactory distribution of the dye and/or the poison throughout the pelvic viscera (Fig. 8). This procedure had some



Fig. 7. Radiograph during bilateral hypogastric artery perfusion with hypopaque. Note the distribution of dye and the evident collateral.

advantages in that it could be repeated with greater ease than the laparotomy; it could be utilized in patients in less satisfactory clinical condition; and it would make possible in the future the utilization of repeated treatments at frequent intervals. The disadvantage of this procedure is that the dye and presumably the cyanide are not as well concentrated in the tumor as when direct intrahypogastric artery injection is carried out. This is under current study and will be reported later. A few patients were treated by systemic (antecubital vein) infusion.

It was with great reluctance that we approached this problem for reasons which I believe are apparent from our cultural antipathy to cyanide. However, from a study of the effects of this agent on several of the larger laboratory animals and the establishment of multichannel monitoring systems, it

appeared feasible to cautiously undertake this venture. Although the antidotes of sodium thiosulfate and sodium nitrite were constantly available in the operating room for immediate administration into an open vein, they were unnecessary at any time. The patients were anesthetized with barbiturates and were then managed by an intratracheal tube and gas-oxygen-ether mixtures. Moderately deep anesthesia was obtained and adequate base lines on the monitoring systems were observed.

When regional perfusion was to be employed, the appropriate vessels were cannulated and radiographs made to ascertain the probable vascular distribution of the cyanide.

The cyanide was freshly prepared in saline at 1 mg. per cubic centimeter and the infusion was calculated at between 0.75 and 1.0 mg. per kilogram of body weight. The rate of infusion was determined by the clinical response of the patient, and it varied between 5 and 15 minutes. When the hypogastric artery cannulization was employed,



Fig. 8. Radiograph during retrograde femoral artery catheterization and perfusion with hypopaque. There are bilateral pneumatic cuffs on thighs.

simultaneous bilateral infusion was utilized.

Following the infusion any indicated operation was carried out, the wound closed, and the patient returned to the recovery room and ultimately to her bed.

As indicated, the patients selected for this procedure were those in whom the disease was considered too far advanced to be amenable to the usual forms of therapy. For the most part, they were patients with carcinoma of the cervix but the series included 1 patient with extensive choriocarcinoma and 2 with endometrial carcinoma (Table III).

All patients exhibited visible tumors that were amenable to biopsy so that the effect of the cyanide could be determined by serial studies. Two of the patients represented late radiation failures, and the interpretation of the tissue changes was unsatisfactory because of the radiation effect in the biopsy specimens.

From these studies, certain observations were made. It was at once apparent that the regional perfusion with cyanide was much better tolerated than the systemic perfusion and that larger doses and more rapid injection could be employed. It was further observed that the toxic reactions associated with cyanide infusion could be ameliorated with anesthesia and were promptly controlled by the slowing or discontinuance of the infusion process.

The recovery and convalescence of these patients treated with sodium cyanide was indistinguishable from that of patients who had not received cyanide. There was no observable delayed clinical toxicity. All patients recovered promptly from the cyanide treatment and no latent or residual effects could be noted.

The changes within the tumors themselves were somewhat more difficult to interpret. We could not detect any clinically significant changes in these patients. Several patients died in a relatively short time (from 2 weeks to 2 months), and during this interval we were unable to detect any clinical reduction in the size of the tumor or in the metastatic mass or increased softening or mobility of the pelvic tumor.

Table III. Patients treated with cyanide perfusion

Patient	Malignancy	Cyanide		Results
		mg./min.	Route*	
S. W.	Cervix (III+)	40/8	Pelvic	Dead 4 months
R.	Endometrial	80/12	Pelvic	Dead 5 months
E. W.	Cervix (IV) post radiation	60/5	Pelvic	Dead 2½ months
O. W.	Endometrial post radiation	80/6	Pelvic	Alive
Z. R.	Cervical stump (IV)	80/8	Systemic (I.V.)	Dead 4 months
L. G.	Choriocarcinoma	50/5	Femoral	Dead 19 days
G. H.	Cervix (IV)	50/17	Femoral	Alive

*Pelvic = bilateral hypogastric artery; systemic = antecubital vein; femoral = retrograde above bifurcation of aorta.

The biopsy material, however, showed rather interesting changes not incompatible with those found in the mammary tumors of dogs. As indicated above, in irradiated patients the previous radiation obscured any changes which we could identify. However, in the nonradiated patients there were cellular changes of nuclear pyknosis and vacuolization and disintegration of cells which appeared in the second to fourth week following the cyanide therapy. Continuing biopsies, however, showed a disappearance of these changes, indicating that these were probably transient in nature (Fig. 9). It is impossible to say from the data available whether the cancer cells were only temporarily affected by this process and recovered or whether this represents a function of random sampling in a small series. We have under trial at the present time—not included in this report—serial or weekly therapeutic efforts with cyanide, to determine whether a more definitive effect can be observed similar to that seen in the mice, i.e., an intensification of effect from serial treatments.

Comment

This is a preliminary report of another agent in the chemotherapeutic armamentarium and includes studies on both laboratory animals and patients. The effects upon Ehrlich's ascites tumor and Sarcoma 180 are significant and easily reproducible. These effects seem to be produced by a mechanism, while not clear, that is different from that of irradiation, alkylating agents, or the anti-metabolites. It is our belief that the action of this agent is probably the inhibition of the cytochrome oxidase enzyme system. The role

of the anesthetic is difficult to evaluate but it is believed that its function is primarily in the lessening of the acute toxic effects and convulsions incident to the intravenous injection of the cyanide itself.

Very evident in these studies is the tremendous variability in the response of the several types of tumors and animals utilized. While the result with the mice on transplantable tumors is more dramatic and is easily subjected to controlled observation, the very fact of their transplantability may place them in a different category of tumor than the spontaneously appearing tumors in larger animals.

The criteria for the degree of malignancy in both dog tumors and the Ehrlich's ascites tumors are under question. However, the metastatic tumors appearing in these animals seem to approach the human criteria for malignancy.

Control studies with the larger animals are most difficult to establish and to interpret. It is regrettable that there is no suitable center where dogs and other domestic animals with spontaneously appearing tumors can be centralized and observed for the various therapeutic effects to be studied. The loss to clinical medicine of these animals every year is a grave one. It is suggested that the establishment of such a centralized area would be an appropriate function for one of the many cancer investigating agencies.

Biopsy control of the spontaneously appearing tumors in dogs is not a satisfactory method of evaluation. However, the clinical changes in the tumors plus the histologic evidence, when correlated with the estimated survival, offer some suggestion of clinical

usefulness. The fact that the mammary tumors of the dog are subjected to some of the same estrous stimulating changes seen in the uterus of women also makes these observations attractive.

Finally, the spontaneous tumors in dogs in many regards parallel human cancer in that they appear in approximately the same relative age groups; the animals have the same environment as their masters; and the hereditary background of the animal in most circumstances is as heterogeneous as that in the human family. The fact that these tumors are spontaneous in origin and generally are not transplantable likewise places them in a category analogous to those of the human. However, the postoperative care and follow-up of these animals is most difficult, and this renders controlled or statistical observations considerably less reliable.

These observations to date indicate that, for those chemotherapeutic agents which do not exhibit chronic toxicity, such as cyanide, the pelvic perfusion without extracorporeal systems is a valuable and useful procedure that can be done easily without elaborate equipment and that the convalescence of the patient is without complications. Because of the ease of utilizing the femoral artery approach, it seems possible to explore, in humans, the multiple therapy series, which exhibited a superior response in mice.

Summary

1. This is a preliminary report on the studies of another cancer chemotherapeutic agent, sodium cyanide, which appears to be an antienzyme type of agent.

2. Simplified techniques for regional pelvic perfusion suitable for agents without chronic toxicity have been developed, and a control of the distribution of the agent can be observed by a radiographic technique.

3. These observations indicate that sodium cyanide anesthetic mixtures are reasonably well tolerated without evidence of chronic toxicity or cumulative effect.

4. Suggestive evidence is presented that differential tumor toxicity is obtained and is manifested by a prolongation of survival time

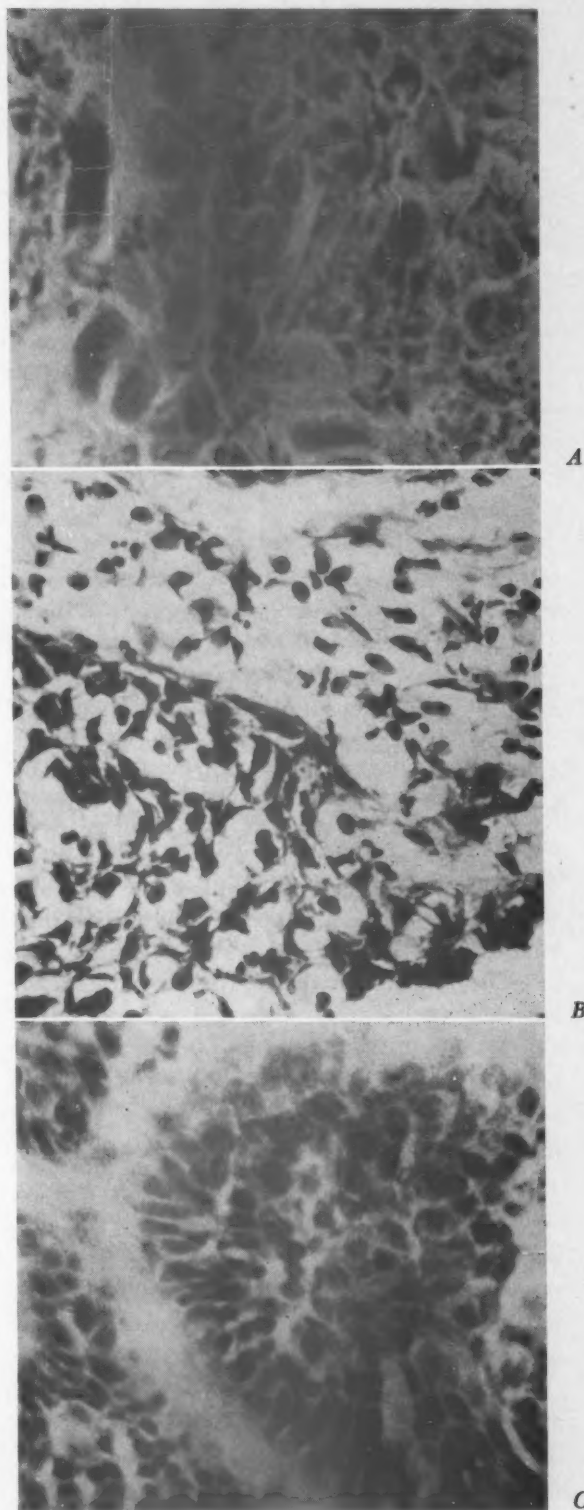


Fig. 9. Representative photomicrographs of biopsy specimens taken from patients treated with cyanide and anesthesia, showing cellular and nuclear changes. *A*, First week post treatment. *B*, Maximum reaction (third to fourth week post treatment). *C*, Recovery (6 weeks post treatment).

in experimental animals and by cellular changes in clinical tumors.

5. These studies are being continued to learn the effect of serial treatment with sodium cyanide in gynecologic malignancy.

REFERENCES

1. Karczag, I.: *Klin. Wchnschr.* 6: 1382, 1927.
2. Warburg, O.: *Science* 123: 309, 1956.
3. Chance, B., and Hess, B.: *Science* 129: 700, 1959.
4. Quastel, J. H., and Rickis, I. J.: *Nature* 183: 281, 1959.
5. Maxwell, L. C., and Bischoff, F.: *J. Pharmacol. & Exper. Therap.* 49: 270, 1933.
6. Perry, I. H.: *Am. J. Cancer* 25: 592, 1935.
7. Galkin, V. S.: Chapter on Narcosis, Medigex, Moscow, U.S.S.R., 1940.
8. Meduna, L. J.: Personal communication.
9. Stone, J. E., Wood, C. D., and Smith, A. N.: *Proc. Soc. Exper. Biol. & Med.* 101: 367, 1959.
10. Smith, A. N., Stone, J. E., and Wood, C. D.: *Pharmacologist* 1: 79, 1959.

Discussion

DR. JOHN A. WALL, Houston, Texas. Only 25 years have passed since the presence of cancer cells in the peripheral blood was described in an article by Poole and Dunlop. Little significance was attached to these findings until Southwick, Packard, Roberts, McGrew, and Cole published their article in 1954 reporting cells in the venous blood draining a carcinoma of the rectum. This has added a tremendous impetus to the search for a systemic chemotoxin. Cole and associates have reported showers of cancer cells in blood specimens incident to manipulation of the tumor by even pelvic examination as well as after dilatation and curettage.

The full significance of cancer cells in the blood is not known. There probably is a time when cancer cells may appear and yet be destroyed by the patient's natural defenses, but at other times the patient's resistance may be low, the cells may multiply, metastasize, and cause death. Moore, Sandberg, and Watne believe "probably 99.9% of all tumor cells released into the blood stream fail to survive and establish metastases."

Karczag, in 1927, described the application of sodium cyanide as an anticancer drug and now 33 years later Dr. Brown reports its clinical application. Chemotherapy is the result of a blending of the specialties, and in this study the combination of anesthesia and a cell-toxin has made the latter a practical therapeutic agent. Dr. Brown reports a unique sequential histologic study of tissues affected by this cell poison. He also has found it unnecessary to extract the pool of toxic substances at the completion of the therapy. This is capitalizing on the fact that it has been impossible to completely isolate the

We wish to express our appreciation to Dr. L. Seager, Professor of Pharmacology, and Dr. J. E. Stone, for their advice and counsel, and to Dr. C. Shafer, Professor of Anesthesiology, and his staff for their assistance in this project.

pelvis for perfusion, and it represents a practical compromise. The use of the femoral vein permits repeated treatments since an extracorporeal system is unnecessary. We can anticipate interesting reports to follow by Dr. Brown and his group relative to the time-dose relationship.

Sodium cyanide offers promise in that there seems to be no accumulative effect on normal tissues and yet there is a certain amount of specificity. This agent, in combination with anesthesia, is a valuable contribution because of the apparent rapid detoxification of the sodium cyanide in the liver. The anesthetic may also aid in suppression of convulsions.

Confusion exists in a study of the complex data submitted regarding practical application of chemotherapy. Approximately 20 products are in general use and about 100 others in preliminary clinical testing stages. Chemotherapy may become a practical adjunct to surgical or radiation treatment of cancer, even in the early lesions, and it is a ray of hope for the future. At present, chemicals have arrested cancer but have not cured it. We believe specific chemotherapeutic agents for individual tumors may eventually become available for clinical application. Chemotherapeutic agents discovered thus far are generally feeble and brief in their effects, but the accumulation of information by such efforts as presented here assures us the picture will change as more specific drugs become available.

DR. BROWN (Closing). As indicated, we intentionally selected patients whose diseases were not amenable to other forms of therapy. We think we may be on the track of a tool which, when explored, may give us a useful adjunct to the usual forms of therapy.

Distribution of metastases in Stage I carcinoma of the cervix

A study of 66 autopsied cases

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THE present knowledge of what influences the dispersal pattern of epidermoid carcinoma of the cervix uteri is singularly incomplete. Although the route of a malignant embolus can occasionally be retraced, it is impossible to foretell when or where the primary malignant nidus will metastasize. From the observations based on this relatively small series of cases, it is evident to us that malignant cells can spread in the so-called tissue spaces, bypass major node groups, and involve nodes completely unrelated to the expected routes of lymphatic spread. The claim that the clinical status of cervical carcinoma can be estimated without a thorough microscopic examination is not unlike the claim of a system for winning at roulette (Fig. 1). Cancer cells, like the marble on the spin of the wheel, may fall unpredictably into one of many slots. Our observations tend to support the aphorism of Celsus that "only the beginning of cancer admits cure" and to discredit the widely accepted concept that a "small cancer" is invariably synonymous with an "early cancer."

Material and method

The 66 cases of epidermoid carcinoma of the cervix uteri herein reported include (A)

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*Presented at the Eighty-third Annual
Meeting of the American Gynecological
Society, Williamsburg, Virginia,
May 30-June 1, 1960.*

22 untreated cases with the primary lesion estimated at 1 cm. or less in diameter; (B) 27 untreated cases with the primary lesion estimated at more than 1 cm. in diameter but grossly confined to the cervix; and (C) 17 treated cases, classified as clinical Stage I lesions following a careful review of all the available records and material.

These cases, collected over a period of 27 years, represent the combined interest and enthusiastic effort of many pathologists throughout California, Nevada, and Arizona. In no instance was death attributed clinically to the cervical lesion, which in most of the cases was not suspected or recognized until necropsy. In most of the cases the size, the location and character, and the probable clinical status of the disease was designated prior to the fixation of the specimen. The status of the cervix in the cases in this report is based on the microscopic examination. The submitted specimen included the genital organs with 1 to 2 inches of the vaginal wall, the bladder and ureters, and all of the removable tissue, vessels, and nerves. In other words, all of the potentially malignant sites and routes were removed en bloc.

The isolation and identification of the lymph nodes and channels in the fixed specimen are difficult, and, except for the major nodes, admittedly not always complete. Our plan of study includes blocks, not only of the major node groups, but of specified areas considered most likely to include the large and small lymphatic vessels and as many of the intervening nodes as possible.

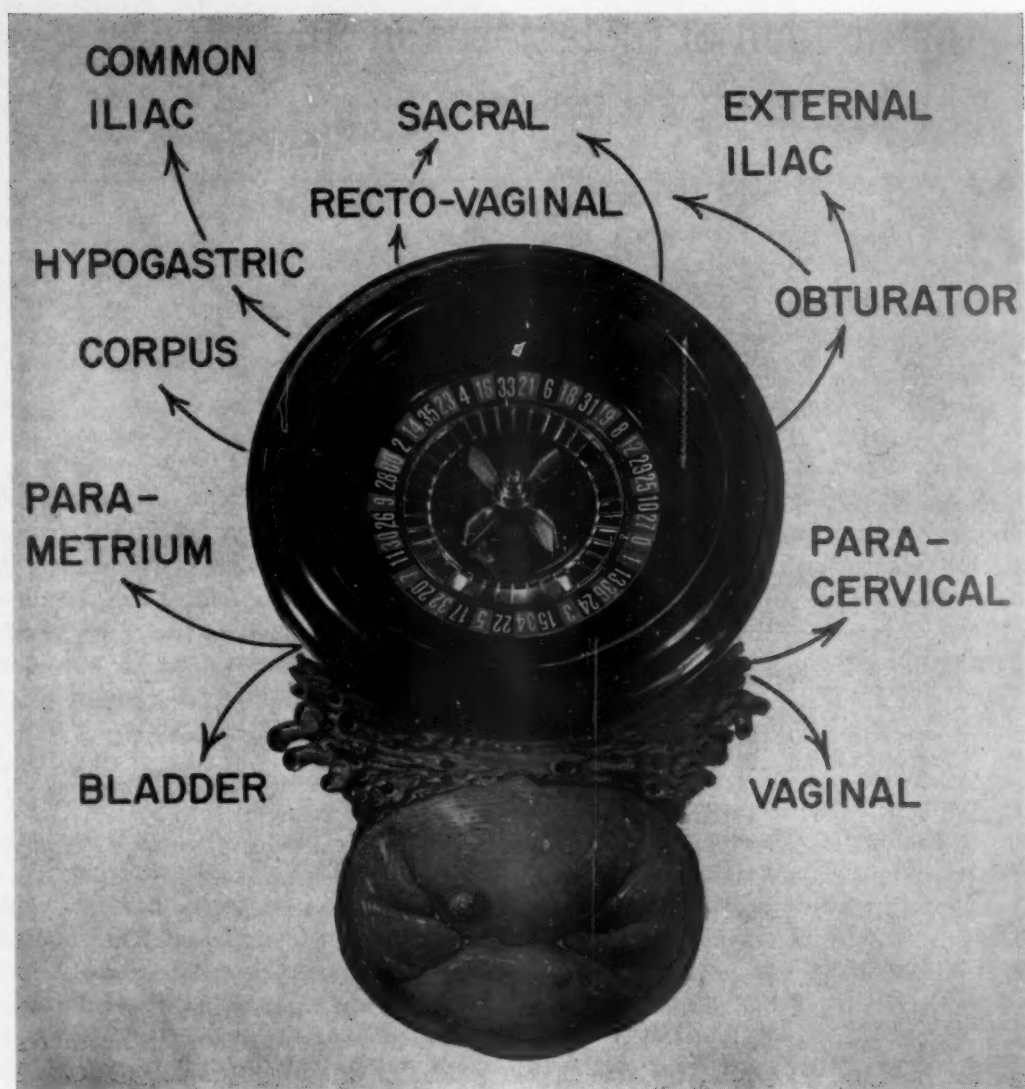


Fig. 1. When, where, or how a malignant nidus extends may be preordained but with our present knowledge is not predictable.

Perturbed by the frequent appearance in the literature of such phrases as "meticulous lymphadenectomy," "meticulous excision of all of the lymph nodes," etc., we have carefully studied their misleading implications. We have estimated, on the basis of many studies, that a "meticulous" removal of all of the pelvic nodes is impossible. We also hold that the term "en bloc excision" does not apply to even the most radical type of pelvic operation. We have further estimated that a truly complete study of the pelvic lymphatic system would require a minimum of 100,000 slides.

The individual case study in this series is limited to an average of 300 tissue blocks and 1,900 slides, with an average of 4 sections to each slide. This does not include the blocks and slides of the cervix and the uterus. In most cases, the cervix had been blocked by the original examiner, and our routine plan of study was necessarily modified. When possible, the cervix was cut into 18 longitudinal blocks and an effort was made to include the three surfaces of the section on each slide.

This material will be examined more completely, to determine the nature and inci-

dence of vessel and tissue space spread within the confines of the cervix, and will be described in a later report.

Ninety-four cases were studied, 28 of which are not included in this report. In 8 of the 28 cases, the material was either incomplete or improperly fixed; 17 were reclassified as Stage II; and 3 cases were diagnosed as adenocarcinoma of the cervix. Discarding the incomplete cases, the incidence of error in the estimate of the gross extent of the disease by competent pathologists was 23 per cent.

Anatomical findings

The difficulties encountered in attempting to correlate the limited reports on this basic problem are enhanced by terminological non-conformity. In our preliminary report¹ the major nodes were classified as primary and secondary groups. This classification, while neither original nor completely satisfactory, did not presuppose an orderly metastasis. We have no desire to perpetuate the terminological discord but any major changes in our classification would negate much of the study. However, this study has emphasized the need of minor changes in an effort to define more clearly the importance of the lymphatic system.

1. The primary group of lymph nodes.

A. Parametrial nodes. There is a marked divergence of opinion relative to the extent of the parametrium. We have included a wedge of endopelvic fascia extending from the cervix to the lateral pelvic wall. This also includes the lateral portion of the paravaginal tissue. The floor and lateral wall of the pelvis are left clean of any fatty tissue, possible nodes, vessels, nerves, and the ureter. The lower portions of the parametrium merge with the peritoneum of the cul-de-sac, the sacral pelvic fascia, the obturator fascia, and the rectum.

In approximately 80 per cent of the untreated cases, 1 to 5 small nodes were demonstrated in the parametrium.

B. Ureteral (paracervical) nodes. One small node is usually located near the uterine artery as it crosses the ureter. In approximately 30 per cent of the untreated cases, one

to three small intercalary nodes were also identified.

C. Vesicovaginal zone. The demonstration of true lymph nodes in this area is difficult, although very small intercalary nodes and small lymphatic vessels are observed in the majority of untreated cases. The spread along the tissue spaces is also an important means of extension. Although this is not a major nodal group, its importance in the dispersal pattern of cervical cancer merits its inclusion.

D. Rectovaginal zone. A true lymph node was demonstrated in only one case in this study, whereas small nodes, interpreted as intercalary in type, were noted in one third of the untreated cases. The large posterior lymphatic channels, richly linked with intercommunicating smaller channels, tend to follow the uterosacral folds to drain eventually into the sacral nodes (Fig. 2). Their possible drainage into the perirectal lymph nodes was not studied.

E. Hypogastric nodes. Varying from 4 to 9 in number, these nodes lie along the course of the hypogastric vein near its junction with the external iliac vein. Occasionally, one or more of these nodes will be found under or between the hypogastric artery and vein.

F. Obturator nodes. Usually described as one large node (Leveuf's node), it is not uncommon to find from 1 to 4 smaller nodes imbedded in the fatty tissue within the obturator fossa.

G. External iliac nodes. These nodes vary from 3 to 8 in number and usually lie on the groove between the external iliac artery and vein.

2. The secondary group of lymph nodes (Fig. 3).

A. Sacral nodes. Lying in the sacral concavity and on the sacral promontory, the 4 to 9 nodes forming this scattered group are usually small and easily overlooked. The small nodes situated low in the uterosacral folds and in the perirectal tissue are not included in this study although their importance is fully appreciated.

B. Common iliac nodes. The 4 to 9 nodes of this group lie on the mesial and lateral

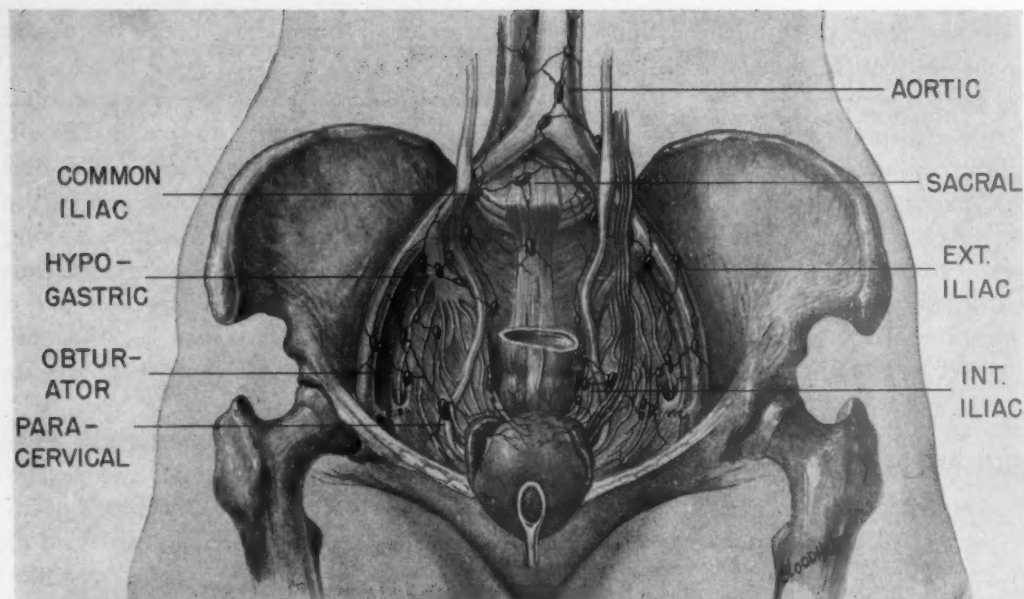


Fig. 2. Lymphatic vessels and nodes of the cervix emphasizing the importance of the recto-vaginal area.

surfaces of the common iliac vessels just below the bifurcation of the aorta.

C. Inguinal nodes. These include the deep and superficial femoral nodes and are not included in this study.

D. Aortic (periaortic) nodes. These uniformly large nodes extend from the level of the bifurcation of the aorta to the diaphragm. They usually lie on the superior and lateral surfaces of the aorta, but it is not uncommon to find them located deep in the aortic-vena cava sulcus.

3. The lymphatic vessels. The routes of the major lymphatic vessels are fairly constant, whereas there are marked variations in the size and the number of the lesser vessels. The larger vessels are readily recognized, but the correct identification of the smaller vessels, especially in the treated case, is difficult and at times impossible.

Studies following the preoperative intra-cervical injection of a nonirritating dye,* have demonstrated a peristaltic-like action of a major lymphatic vessel in 3 of 27 prepared cases. The failure to demonstrate this phe-

nomenon in all of the prepared cases is readily explained by (1) the mechanical difficulties encountered in the exposure and the visualization of a major lymphatic vessel, and (2) the inconsistency of dye dispersal.

Admitting the risk inherent in advancing a theory based on limited observations, we suggest that a sluggish but definite peristaltic-like action is characteristic not only of the major ones, but of all the lymphatic vessels containing valves. The lymph is propelled by the weak contractions of the thin layer of smooth muscle present in the vessel wall. However, this inadequate muscle layer does not explain the visible contractions. Careful dissection and examination demonstrate a definite increase and hypertrophy of the muscle fibers at the level of the lymphatic vessel valve. This increase in muscle body accounts for the knobby or beadlike appearance of the lymphatic vessels and could readily explain the visible contractile activity. The full importance of any factor or factors potentially capable of stimulating this action needs to be considered in order to understand more completely the dispersal patterns of a malignant embolus.

4. The effect of radiotherapy upon the

*Pantomine Sky-Blue, E. I. du Pont de Nemours & Co., Inc.; Direct Sky Blue, Wyeth Laboratories, Inc.

nodes. Our observations permit four premises regarding the status of the pelvic lymph nodes: (1) an enlarged node does not invariably harbor malignant cells; (2) innumerable variations in the cellular patterns and distortions of the intranodal architecture may occur in the absence of malignancy, irradiation, or inflammation; (3) the basic function of the lymphatic node in the presence of cervical carcinoma, in spite of the theories and conjectures, is not entirely clear; (4) the erratic dispersal patterns of malignant emboli emphasize the futility of predicting their presence or absence except by the careful examination of all potential routes and sites. Any other approach, regardless of the investigator's experience, borders on geomancy.

Our material demonstrates a variation in the number of nodes in the untreated and the treated cases. However, the exact implication of this variance is not clear. There are certain technical flaws in the examination of a fixed specimen. The isolation and identification of the smaller nodes is difficult and admittedly incomplete in the fixed specimen of the untreated case. The technical difficulties and the probabilities of error encountered

in the fixed specimen of the treated case are increased many times.

How rapidly a node responds to the "trauma" of acceptably effective radiation is not revealed in this series. However, it is evident that all nodes of the same anatomical position do not react in the same degree; nor is it possible to examine a node and unequivocally interpret the cellular changes as evidence of therapy response. The nodal changes noted in the untreated cases can be as extensive as those found in the treated case. It is apparent that neither the size of the node nor its location within the perimeter of accepted radiation activity explains the presence or absence of node response.

The nodes present in the untreated cases display a marked variation in size, consistency, and morphology. The reticular and lymphoid proliferation, or so-called hyperplasia, varies with the presence of a pelvic inflammatory process, sometimes with fibroids, with the history of possible intra-abdominal bleeding due to many causes, or, not infrequently, with no demonstrable cause. It is therefore frequently difficult to classify the normal from the abnormal lymph node.

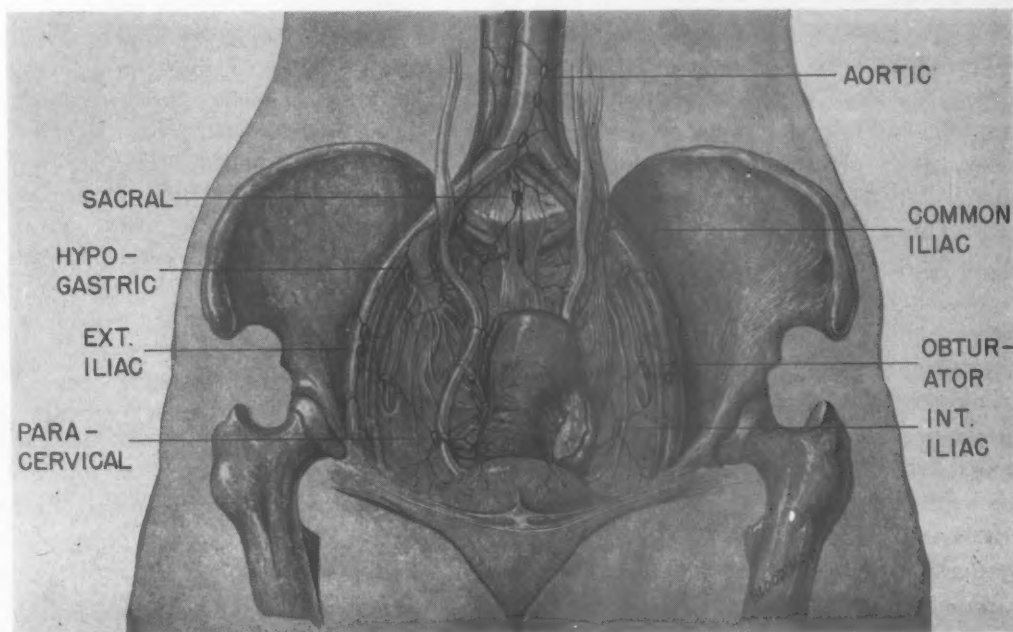


Fig. 3. Lymphatic vessels and nodes emphasizing the importance of the anterior area.

Table I. Incidence of malignant spread and sites in 66 cases of cervical carcinoma, clinical Stage I

	Parametrium		Paracervical		Vesico-vaginal	Recto-vaginal	Obturator	
	Right	Left	Right	Left			Right	Left
Group 1 Untreated, 1 cm. or less (22 cases)	—	1	1	—	1		2	—
Group 2 Untreated, over 1 cm. (27 cases)	1	1	—	1	2	1	3	1
Group 3 Treated (17 cases)	—	—	—	—	—	1	1	1

The nonmalignant node may vary in size from an estimated 1 mm. to 2.5 cm. in diameter, whereas in the irradiated case the nonmalignant nodes tend, on the average, to be smaller. The consistency also varies, and the "stony hard" node is not invariably a malignant node. In the majority of the nodes displaying an increased firmness, it is usually possible to demonstrate intranodal hyalinization, fibrosis, and even calcification. The identification of active malignant cells within a node is not difficult, but the certain interpretation of nodes containing "shadows" or "ghosts" suggestive of destroyed cancer cells remains difficult despite the use of many types of histologic stains.

We have also changed our previous ideas concerning the importance of matting of the nodes and perinodal adhesions. It was our original impression that these changes were almost invariably pathognomonic of malignancy, but in 3 of the untreated cases both matting and adhesions were noted in the absence of any demonstrable pelvic or abdominal disturbance.

5. The intercalary nodes. The incidence of intercalary, pseudo-, or anomalous nodes is so common as to merit a separate classification, if for no other purpose than to stress their importance. Although they are found in close proximity to the major vessels, they are more frequently located in the tissue coursed by the lesser channels. Their presence or absence does not seem dependent on the age of the patient or the pathologic status of the pelvis. Whether they are more radiosensitive is difficult to state. The marked variation in the size of these struc-

tures increases the possibility that many are overlooked, especially in the treated specimens.

Pathology findings

1. Untreated cases. Forty-nine untreated cases of squamous cell carcinoma of the cervix uteri in which the patients died of causes unrelated to the cervical lesion were studied at necropsy.

Group A. Twenty-two cases with the primary lesion estimated at 1 cm. or less in diameter. Microscopic evidence of spread was noted in the following 3 cases (Table I).

Case 1 (0-1-7-37). White; single; age 28 years. Cause of death, virus pneumonia. Small intercalary node, left parametrium. All nodes uniformly enlarged. Total nodes studied, 84.

Case 2 (0-1-17-49). Negro; gravida iv; age 39 years. Cause of death, accident. Small right paracervical node; one large right obturator node. Extensive old pelvic inflammatory disease. Total nodes studied, 91.

Case 3 (0-1-9-42). Negro; gravida iii; age 33 years. Cause of death, cardiac. Two small malignant emboli in the anterior channels: one small right obturator node; one right hypogastric node. It is possible that one of the small nests of malignant cells was lying free in the tissue space. Total nodes studied, 78.

Group B. Twenty-seven cases with the primary lesion estimated at more than 1 cm. in diameter but considered limited to the cervix. Spread was demonstrated in the following 6 cases (Table I).

Case 1 (0-1-36-52). White; gravida vi; age 50 years. Grade III. Cause of death, cardiac. One

Hypogastric		External iliac		Common-iliac		Sacral		Aortic	Distant metastasis	Total
Right	Left	Right	Left	Right	Left	Right	Left			
1	-	-	-	-	-	-	-	-	-	3 cases (13%)
1	3	1	1	-	-	-	-	-	-	6 cases (22.2%)
1	2	2	1	-	1	-	1	1	-	4 cases (23.5%)

small node, right parametrium; small malignant "nest" in anterior tissue space; one node right obturator group; one right external iliac node. Total nodes studied, 84.

Case 2 (0-1-49-56). White; gravida ii; age 45 years. Grade III. Cause of death, postcholecystectomy. Marked edema of all of the pelvic nodes and channels. One right obturator node; one right hypogastric node. Total nodes studied, 87.

Case 3 (0-1-23-51). Negro; gravida iv; age 31 years. Grade II. Cause of death, accident. Bilateral tuboovarian inflammatory abscesses, multiple fibromyomas. One small intercalary node, left parametrium; one left paracervical node; one large external iliac node. Total nodes studied, 68.

Case 4 (0-1-25-52). White; gravida ?; age 55 years. Grade III. Cause of death, suicide. Bilateral chronic pelvic inflammatory disease, fibromyomas. One small "nest," left anterior area; 2 small left hypogastric nodes; marked benign thickening of the parametrium with uniformly enlarged pelvic nodes and channels. Several node groups displaying marked matting. Total nodes studied, 73.

Case 5 (0-1-51-57). White; gravida iv; age 44 years. Grade II. Cause of death, diabetes. Extremely obese. Many of the nodes edematous. One left obturator node. Total nodes studied, 50 plus.

Case 6 (0-1-8-41). Negro; gravida "many"; age 63 years. Grade II. Cause of death, cardiac. Unusually large veins and arteries. Numerous nodes with marked hyaline changes; one right obturator node; one left hypogastric node. Total nodes studied, 93.

Positive parametrial nodes and demonstrable spread in the tissue spaces are not uncommon in the later stages of the disease. However, similar observations in the Stage I

cases are difficult to demonstrate. Thus, the assumption frequently made that the emboli can readily pass through the parametrium appears logical. Unfortunately, the flaw in this statement is the finding of a small positive node in one case following the careful examination of the twenty-second block of the parametrium. In this series, the average number of blocks of each parametrium was 10, with an average of 4 sections per block. If the number of blocks had been increased twofold I am certain that a higher incidence of parametrial involvement would have been found.

The sites of metastases observed in this series emphasize the unpredictability of the dispersal pattern.

2. Treated cases. Seventeen treated cases of squamous cell carcinoma of the cervix in which the patients died of causes unrelated to the cervical lesion were studied at necropsy. In each of the 17 cases, the gross and microscopic description of the cervical lesion and the palpable findings prior to irradiation permitted their classification as Stage I in extent. However, on the basis of a demonstrated error of 23 per cent, it is probable that at least 4 of the 17 cases would, if treated surgically, be reclassified into a higher bracket. Evidence of spread was found at autopsy in 4 cases.

Case 1 (R-1-5-41). White; gravida iv; age 47 years. Grade III. Cause of death, nephritis and diabetes 4 years after irradiation. One large left hypogastric node. Cervix negative. Total nodes studied, 47.

Case 2 (R-1-11-49). White; gravida ii; age 38 years. Grade II. Cause of death, alcoholism (?)

2 years after irradiation. Several small "nests" in the right rectovaginal chain; one left sacral node. Total nodes studied, 63.

Case 3 (R-1-14-57). White; gravida iii; age 44 years. Grade II. Cause of death, Hodgkin's disease 7 years after irradiation for the cervical disease. Cervix negative. One left obturator node; one left hypogastric node, 2 left external iliac nodes, 2 small left common iliac nodes, and 3 aortic nodes just above the bifurcation. One large right inguinal node and 2 large common iliac nodes diagnosed as "Hodgkin's disease." Total nodes studied, 59.

Case 4 (R-1-17-59). Negro; gravida viii (?); age 41 years. Cause of death, primary malignancy, brain 4½ years after irradiation. One right obturator node, one right hypogastric node, and 3 right external iliac nodes. Cervix, positive. Total nodes studied, 48.

The most impressive difference between the treated and the untreated cases is the decrease in the number of identified nodes after irradiation. In each case the course of therapy had been carefully reviewed and accepted as adequate. However, as previously noted, the isolation and identification of the smaller nodes in the treated cases is difficult. Another observation was the decrease in the number of blood and lymphatic vessels, a reaction that could affect the dispersal pattern and rate of the cancer.

Comment

This study was started in 1932, at the instigation of the late Dr. William G. MacCallum, professor of pathology at the Johns Hopkins School of Medicine. The original plan included the tracing of the pelvic lymphatic channels, the location and general pattern of the node groups, and the incidence of lymph node metastases in cervical cancer. The study was to be completed in one year, but 27 years of continued investigation have not unraveled the vagaries of this complicated system. However, a few observations occasionally difficult to substantiate fully, are of enough importance to warrant further comment.

1. The primary lesion. It is evident that neither the size nor the gross character of the primary lesion unequivocally determines

its dispersal pattern. Although the successful dispersal of intracervically injected dye tends to follow predictable routes in the normal pelvis, this uniformity is not noted in the presence of either benign or malignant pathology.¹ It is not possible from this series to correlate the cellular index of the tumor or the age and parity of the patient with the incidence of spread.

2. The parametrium. One of the most difficult diagnostic problems in the management of this disease is the clinical evaluation of the parametrium. Thickening, secondary to benign processes, is frequent, and misinterpretation is common. The so-called characteristic parametrial thickening due to malignant extension is unreliable even when reported by the most experienced clinician, and the needle biopsy has not fulfilled the expectations originally predicted. The reported discrepancies in estimation of parametrial involvement can in part be explained by the amount of tissue interpreted as constituting the parametrium, and in part by the thoroughness of the examination. It is also possible that nests of malignant cells can travel along the so-called tissue spaces. However, it is not difficult to demonstrate the presence of lymph channels coursing the parametrium unhindered by nodes. Thus it is logical to theorize that an embolus can readily course the parametrium and involve other regional node groups. The suggestion that the involvement of the parametrium usually occurs after the appearance of more distant metastases may be correct in the occasional case, but we do not think it accounts for the majority. It appears reasonable to conclude that the increase in parametrial involvement is consistent with the natural history of the disease and not dependent on an explanation of retrograde spread. We are further convinced that a more thorough examination of the parametrial tissue would have revealed a higher frequency of metastases than reported here. It is also probable that a more complete study of the lateral paracervical and paravaginal tissue, not uniformly included in the parametrial specimen, would reveal a higher incidence of free spread. This

has been emphasized by the giant section studies recently described by Parsons, Friedell, and MacMillan.²⁻⁴

3. The lymphatic channels. Variations in the caliber and the wall thickness of the lymphatic vessels are readily demonstrated in the unfixed specimen. However, in the fixed specimen, regardless of the fixative agent employed, the identification and evaluation of the lesser channels is tedious, difficult, and admittedly inadequate. Thus, any attempt to trace these routes with our methods of study reflects the uncertainty inherent in trying to complete a puzzle with the majority of pieces unavailable.

When identifiable lymphatic vessels in the treated and the untreated cases are compared, it is apparent that there is a definite decrease in the number of vessels in the treated case. A larger incidence of partial and complete vessel occlusion was also observed in the treated cases. Unfortunately, this vessel change is not consistent in individual cases at the same anatomical level and does not occur in every treated case. It can also be demonstrated to a lesser degree in the nontreated case. Although it is possible that radiotherapy does affect the lymphatic channels of some individuals, we are not prepared to comment on its implications. However, it seems logical to assume that the partial or complete occlusion of a lymph channel serves as an important deterrent to the dispersal of cancer emboli.

Regardless of the simplicity of an operative or diagnostic procedure, the importance of the lymphatic system and its probable reaction to any form of manipulation should be considered. In 1935 we stated that "the dangers of infection, dissemination, or stimulation of tumor growth and hemorrhages are not as dangerous as they were once considered by many. In spite of any possible risks, the data obtained by biopsy more than counterbalance them."⁵ Twenty-five years later we still stress the value of adequate tissue examination, but the dangers inherent in manipulation and infection appear more important. We believe that undue manipulation of the cervix, the presence of an infec-

tion before and/or after biopsy or conization, and pregnancy result in an acceleration of lymph vessel activity. The potential seriousness of these factors cannot be stressed too strongly.

4. The lymph node. According to the literature, the function of the lymph node is "to filter, detoxicate, and sterilize the lymph." The mechanisms involved in these activities are often described, but it is evident that the explanations are inadequate, if not incorrect. Although it is not difficult to identify a malignant embolus, we are still trying to identify the presence of a single cancer cell within the node. Admittedly this is not a simple task, but the law of chance should reveal a few such instances during the examination of a large number of nodes. Assuming that a single malignant cell could be recognized, we are confronted with the question of its intranodal activity. It is impossible to supply facts, but the possibility of a single cancer cell, or even a small group of cancer cells, being destroyed or "sterilized" in the lymph node deserves some consideration. However, the presence of a large malignant embolus may prove too overwhelming for the "sterilizing" action of the node.

Interpretation of the lymph node response of the patients receiving adequate irradiation in this series is incomplete in that most of the patients had lived from 1 to 11 years after treatment. As we have previously stated, the nodes tend, on the average, to be smaller and firmer. There is also an increased number of nodes exhibiting hyalinization, fibrosis, and calcification. Unfortunately, this reaction or response is not consistent in the same case at the same anatomical level. Occasionally the node is completely replaced by connective tissue, a change infrequently noted in the so-called normal nonirradiated node.

Although these changes certainly demonstrate the action of irradiation on the nodes, we are not prepared to explain its apparent failure to affect all of the nodes located within the adjudged area of ray penetration. From our material, two premises are offered: (1) the action of the rays may inhibit the

growth rate of the cancer cells or the fibrosing effect of the therapy may serve as a semipermanent tomb for the encapsulated cancer cells; (2) the atrophic or sclerosing changes affecting both the vessels and the nodes may serve as a deterrent to the spread of cancer. Unfortunately, the interpretation of our material permits only an equivocal answer to the effectiveness of radiation in the treatment of either the primary cervical lesion or the involved lymph nodes.

An interesting but futile effort was made to explain the unpredictable response of the primary lesion and the lymph nodes to radiation therapy. For many years we have contended that the response of cervical cancer to radiation therapy is not predicated upon its morphological status. To explain the response we have resorted to such terms as "biological resistance" and "tissue receptivity." These terms are neither supported nor refuted by our observations.

Recent investigations on the action of various chemotherapeutic agents in the treatment of ovarian cancer have revealed a wide variation of response. Like the response of cervical cancer to irradiation, tumors of the ovary interpreted as identical in morphology and similar in clinical status react differently to the same agent. It has also been observed that the susceptibility or resistance status of the cell appears intimately related to its phase of mitotic activity. Thus, not only must the therapeutic agent with the highest palliative rating and the lowest incidence of side effects be selected, but the timing of the treatment must coincide with the "susceptible" phase of the cancer cell. This is not a new concept, as attempts to predict the radiosensitivity of the cervical lesion on the basis of certain changes in the vaginal cytology are common. There have also been numerous studies relevant to increasing the sensitivity of the cancer cell by the use of hormones, vitamins, diets, and a wide range of chemical agents. These efforts to effect a means of controlling the nuclear activity and possibly holding it in its most susceptible phase offer hope for a new approach in the management of cancer.

The present methods of treatment of cervical cancer, considered in the light of our observations, are not only inadequate but are based on unsound anatomical and physiological evidence. Surgery, despite its being described in such deceptive terms as meticulous dissection, en bloc excision, complete lymphadenectomy and pelvic exenteration, is not the final answer. Neither the estimate of the extent of the disease at operation nor the experience or dexterity of the surgeon inevitably determines the prognosis. The operation, undertaken with the intent of cure, is based not on known facts but on the laws of chance. Theoretically, approximately 80 per cent of the patients with proved Stage I cases should be cured by a total hysterectomy; whereas, except in its most radical form, operation will hold little for the remaining 20 per cent. However, the palliative action of operation deserves some consideration. It is not only possible, but is probable, that cancer cells and involved nodes can be trapped in the scar tissue resulting from the extensive trauma of operation. The duration of entrapment varies but may be for years or, in the rare case, for the life of the patient.

Our observations also emphasize the inaccuracies inherent in the currently accepted methods of reporting the effectiveness of operation and irradiation in the treatment of cervical cancer. For comparative purposes, all cases should be reported according to the preoperative or preirradiation estimate, and not on the grouping established by examination of the surgical specimen. The difference of grouping with the so-called "correcting the records" method is surprisingly high. In this series, there was an error of 23 per cent between the gross and the microscopic estimate of the extent of the disease. These 20 of 86 cases have only one direction to go and that is into a higher bracket. If they were treated radiologically this error would result in a statistical devaluation of irradiation in the treatment of cases in the Stage I group. If they were treated surgically, the error of clinical classification would be corrected to the advantage of the surgical approach.

The original intent of this study was to describe all of the observations in detail. However, any attempt to present the innumerable physiopathologic changes noted in 66 cases would result in confusion. There are too many unexplainable variations which, if the scope of the normal variant were known, probably have no significance. We have tried to limit our reported observations to the reactions and responses of the lymphatic vessels and nodes. This in no way minimizes the importance of spread by continuity through the tissue spaces or by the blood vessels.

Summary

1. A study is presented of 66 cases of cervical cancer in which the patients died of causes unrelated to the cervical lesion, which was classified as Stage I in extent on the basis of microscopic examination of the cervix.

2. Spread of the disease was demonstrated in: (a) 3 of 22 untreated cases with the primary lesion of 1 cm. or less in diameter; (b) 6 of 27 untreated cases with the primary lesion of more than 1 cm. in diameter; (c) 4 of 17 treated cases with the extent of

the primary lesion estimated on the pre-irradiation records.

3. Cancer cells, regardless of the site of the primary lesion, the histologic grade, and the age and parity of the patient, can spread in any direction. The direction and the degree of spread are not predictable.

4. The anterior and posterior spread is almost as frequent as the lateral extension. Thus, any attempt to remove all possible cancer-bearing tissue must include these areas.

5. A peristalsis-like action of the lymphatic vessels was noted and its importance in the dispersal pattern of cervical cancer emphasized.

6. The response of lymph nodes to irradiation is discussed, but the equivocal observations continue to becloud the true effectiveness of this form of therapy.

7. The importance of new observations on the relation of mitotic activity to cancer cell susceptibility as a possible new approach in therapy is discussed.

8. The errors inherent in the present methods of comparing the effectiveness of surgery and irradiation are noted with the suggestion that new ground rules be provided.

REFERENCES

1. Henriksen, Erle: *AM. J. OBST. & GYNEC.* 58: 924, 1949.
2. Parsons, Langdon: Personal communications.
3. Friedell, Gilbert H.: Personal communications.
4. MacMillan, H. J. C., and Parsons, L.: *Merck Sharp & Dohme Seminar Report* 2: 3, 1957.
5. Henriksen, Erle: *Surg. Gynec. & Obst.* 60: 635, 1935.

Discussion

DR. ROBERT A. KIMBROUGH, JR., Philadelphia, Pennsylvania. Dr. Henriksen has brought to us some of the results of his 28 years of study of the lymphatic spread of carcinoma of the cervix.

Our study of removal of the regional lymph nodes as an adjunct to radiation therapy of carcinoma of the cervix was begun in 1951 in the hope of improving the results previously obtained by radiation alone.

Survival rates following radiation therapy are more or less in direct proportion to the usually recognized absence of involvement of the regional lymph nodes in the various stages of the

disease. This fact strongly suggests that few patients who already have nodal metastases become long-term survivors and clearly brings into focus the necessity of more effective techniques of radiation or the surgical removal of the pelvic lymph nodes.

Vaginal and rectal examinations previously were depended upon to make, at best, an estimate of the gross extent of the lesion. Too often such estimates were found later to be inaccurate. It seems reasonable, therefore, that extraperitoneal exploration and regional lymphadenectomy should constitute the first step in the

therapy of cervical carcinoma. Lymphadenectomy can be accomplished more thoroughly and more safely before full radiation therapy is given. Microscopic study of the node-bearing areolar tissue provides information on the extent of the disease. This procedure is followed by the local application of radium and full external roentgen radiation. Our present methods of application of radium yield an estimated cancerocidal dosage to structures 4 cm. lateral to the cervix. Therefore, we are depending upon the local application of radium to destroy the original lesion and on the combination of lymphadenectomy and external roentgen therapy to eradicate the disease along the lateral walls of the pelvis.

During the first 8 years of our study, 64 patients with clinical Stage I lesions have been managed by these techniques. Of these 64 patients 20.3 per cent had demonstrable nodal metastases. The incidence of node involvement in Dr. Henriksen's 49 untreated patients was 18.3 per cent. Of the 23 patients with Stage II lesions, the regional nodes were involved in 8. This high incidence of node involvement seems to justify our present approach.

Of the 23 patients with Stage I lesions who were treated more than 5 years ago, 20 (87 per cent) are well and present no evidence of recurrence; of the 8 patients who had Stage II lesions, 5 are apparently well.

Of the 39 patients with Stage I lesions who were treated more than 3 years ago, 35 (89.7 per cent) are apparently well. Thirteen (72.2 per cent) of 18 patients with Stage II lesions are well 3 or more years after treatment.

Of 7 patients with node involvement treated more than 5 years ago, 2 are living and well. Of 12 patients with node involvement treated more than 3 years ago, 6 have survived from 3 to 8 years without evidence of recurrence.

DR. DANIEL G. MORTON, Los Angeles, California. I should like to compliment Dr. Henriksen on the excellence of his study.

Both the incidence and the significance of lymph node metastasis are of great interest in cancer of the cervix with respect to methods of treatment and prognosis. With the more widespread use of radical hysterectomy and experimental lymphadenectomy, and the regrettably few studies like Dr. Henriksen's, a considerable body of information regarding incidence of node involvement has accumulated during the

Table I. Incidence of lymph node involvement in cervical cancer

Author	Stage I (1,225 cases) (%)	Stage II (827 cases) (%)
Carter	12.7	30.7
Gray	6.9	17.5
Antoine's clinic	8.5	27.9
Kelso	7.7	30.7
Meigs	18.2	32.4
Morton	18.5	38.0
Navatril	11.2	23.1
Mean	11.9	28.6

last 10 to 15 years. Recently I gathered together figures from a number of different sources which I think can be regarded as reliable and representative in spite of the unpredictability of the dispersal pattern. The averages of the percentages were 11.9 per cent for 1,225 Stage I cases and 28.6 per cent for 827 Stage II cases (Table I). I do not understand the extremes above and below the means, but I suppose that individual differences in clinical staging, thoroughness in removal of nodes, and completeness of the study of the nodes might account for them. Reliable figures for Stages III and IV are not available and are of less moment to us because the method of treatment is not affected and because the prognosis is so poor anyway. The figures approach 50 per cent lymph node involvement for Stage III cases and 75 per cent for Stage IV. It seems apparent that Stage 0 cases are going to be associated with node involvement in very rare instances only and for this we can be duly thankful since more and more such diagnoses are being made.

The significance of regional node metastasis is by no means clear except that by and large it

Table II. Five-year survival in patients with nodes involved

Author	Stage I (%)	Stage II (%)	All (%)
Carter			33.3
Kelso	66.6	43.1	50.0
Meigs	41.6	0.9	26.1
Morton			27.7
Mean			34.2
Late results			
Meigs (10 years)			22.7
Morton (10 years)			11.1

means a poor outlook. Figures which I have gathered (Table II) indicate that 5 year survival can be anticipated in approximately one third of Stages I and II patients with regional node involvement who have been treated by radical hysterectomy and removal of the regional lymphatics. However, our experience indicates that if one follows the patients long enough one finds that the majority die of cancer. Meigs reported 22.7 per cent survival in these patients at 10 years, and we had 11.1 per cent 10 year survivors. To us this may mean that cancer cells are being harbored in the lymph nodes by a few for very long periods of time and that bodily resistance may enter into this ability to isolate metastatic deposits for indefinite periods.

The interesting facts to be considered are that some women live a long time with cancer cells in the nodes, even many years, perhaps even the rest of their lives. Dr. Henriksen's findings point up this fact rather vividly. Had they not died of something else, were those women in whom he found cancer metastases many years after treatment going to die of cancer or not? We have all seen instances of prolonged survival, 10, 15 years after treatment and then, finally, death from renewed activity on the part of a metastatic deposit in a regional lymph node. How can this happen? Another interesting observation bearing on this point comes from the recent report from Antoine's clinic in Vienna by Rauscher and Spurny in which they compared the results of the Wertheim operation without systematic removal of lymph nodes with the same operation plus the systematic removal of regional nodes. The results were almost identical, 74 and 75.8 per cent 5 year survivals, respectively. How does one explain this? It seems to me that one is forced to consider the possibility that lymph nodes may serve at times to isolate or entomb cancer cells, perhaps on occasion even indefinitely; to act as a first line of defense as in the case of infections. The nodes are not, in this concept, always successful, of course, and we know that they are more commonly overwhelmed. Knowledge regarding the spread of cancer from its original site has been increasing. We have learned that cancer cells get into the blood stream not infrequently and that this does not always entail a bad prognosis. What happens to these cells? Do they die of their own accord, are they destroyed by some activity of the body, or are they entombed somewhere, as in nodes? Perhaps cancer cells get into the lymphatics far

more often than has been revealed by even such careful studies as Dr. Henriksen's and are destroyed before they can take hold. Indeed there are many similarities between cancer and infection with respect to the manner in which the body reacts to these harmful stimuli. The human body appears to have both a local (the nodes) and a general resistance to both cancer and infection. In regard to general body reaction to cancer it is common to observe a marked improvement in general health when the local disease has been eradicated or destroyed. This concept also permits us to reconcile the tumors of equal extent which react in diametrically opposite ways.

DR. JOE V. MEIGS, Boston, Massachusetts. It is perfectly obvious to anyone doing this work that one cannot dissect the pelvis completely. The only thing I can say is that for some reason in certain cases you do the best dissection you can do and some of the patients will live.

Carcinoma of the cervix is different from carcinoma of the breast. I don't think you can cure carcinoma of the breast. I think cancer of the breast will always recur if the patient lives long enough. Years after the operation if there is a calamity, such as the husband dying or a financial upset occurring, the tumor will come back again, and it will be a tumor identical to the one that the patient had originally. I have seen this happen even 25 years after operation.

Squamous carcinoma is different from adenocarcinoma, certainly with respect to that of the vulva or cervix. It is unusual for a patient to die of carcinoma of the cervix after living without disease for 5 years, and certainly after 10 years it would be quite rare.

Good radiation therapy in the proper case is ideal treatment. I do not feel that surgical treatment is the only way; in many cases, however, operation is essential.

This leads me to Ruth Graham's work. I know this is not accepted by all. It is natural that anyone bringing anything new to light will be criticized, but I must say that recently (and since Ruth Graham has left our hospital Dr. Thomas H. Green and I have carried on a group of cases at Pondville Hospital) our results are coming very close to her predictions. There are differences in patients; some respond to radiation and some do not. We must all realize that we must do our best to select patients for treatment and not insist on everyone's having radiation or

radical hysterectomy and node dissection. I do not believe that any one method is the only kind to use. We should find out what is best for each individual patient.

DR. HENRIKSEN (Closing). A politic move would have been a preliminary report of the findings in the first 2 or 3 cases. Unfettered by the subsequent complex and often contradictory observations, our conclusions could have been presented with an aura of authority.

Ever inherent in a tedious effort of this type is the danger of autohypnosis. Ideas and im-

pressions, originally bordering on pure fantasy, may after many years evolve into accepted facts.

For the past 10 years I have been disturbed with the increasing conviction that we were not getting the full value out of our material. I am certain that we have either overlooked or failed to recognize changes of importance. The need of a wider range of cellular stains was early recognized, but lack of outside financial assistance made this impossible. The basic principles of cancer are, with our present knowledge, not only complex but poorly understood.

Effects of pregnancy and labor on the breathing pattern of the newborn infant

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IN OUR preliminary report¹ a year ago, we analyzed over 600 premature births along with about 175 cesarean sections and about 200 full-term vaginal deliveries. We concluded that the normal breathing pattern for the newborn infant was that shown in Fig. 1. Group I infants were considered normal, and Group II breathing was also assumed to be a normal pattern as there were no deaths in this group. All neonatal deaths during the first 7 to 14 days were in those infants with Group III breathing, which was therefore considered to be an abnormal pattern.

We were so much impressed with these data that we have continued our study and can now report upon some 813 full-term vaginal deliveries, about 800 premature vaginal deliveries, and about 250 cesarean sections. We are presenting these additional data at this time, not because we have many striking new conclusions, but rather because we would again like to express our enthusiasm for this simple method of designating (1) those premature infants in Group III who are in potential danger and who should be most carefully watched, and (2) the other premature infants in Groups I and II whose prognosis is uniformly good and who do not, regardless of size, require such continued

close attention. This saves a great deal of nursing time in the premature nursery.

Because we are convinced that the search for the cause of neonatal deaths should be directed at the cause of Group III breathing, our continuing purpose has been to find those factors in the pregnancy and labor which are followed by abnormal breathing and to assess the relative importance of each. Our present volume of material is still too limited to permit definite conclusions in many categories, and further study is planned.

Effect of prematurity

The greatest single factor resulting in abnormal (Group III) breathing is prematurity (Table I).

The premature infants have been divided into only two groups at the suggestion of Herbert C. Miller, as the babies from 1,500 to 1,745 grams so closely resembled those from 1,000 to 1,495 grams, and those from 1,750 to 1,995 grams behaved almost like

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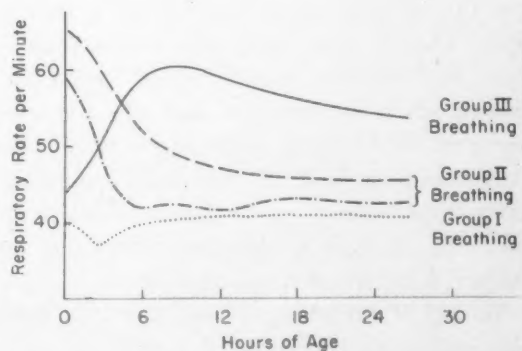


Fig. 1. Breathing patterns in the neonatal period.

Table I. Incidence of abnormal breathing with respect to maturity of babies delivered per vaginam

	<i>No. patients</i>	<i>Groups I and II</i>	<i>Group III</i>	
			<i>No.</i>	<i>%</i>
Full-term	813	764	49	6
Large premature*	653	556	97	15
Small premature†	148	54	94	64

*1,750 to 2,495 grams weight.

†1,000 to 1,745 grams weight.

Table II. Incidence of abnormal breathing in babies delivered by cesarean section

	<i>Groups I and II</i>	<i>Group III</i>	
		<i>No.</i>	<i>%</i>
<i>Full-term</i>			
Vaginal delivery	764	49	6
Cesarean section	180	26	13
<i>Large premature</i>			
Vaginal delivery	556	97	15
Cesarean section	25	13	34
<i>Small premature</i>			
Vaginal delivery	54	94	64
Cesarean section	0	10	100

those from 2,000 to 2,495 grams. The greater the degree of prematurity, the higher will be the percentage of abnormal breathing. That this may not be the whole story will be seen later.

Effect of type of delivery

A second important factor is related to the type of delivery (Table II).

Abdominal delivery evidently results in something like twice as much Group III breathing as vaginal delivery. That this is not the result of anesthesia will be apparent later. That it is not the result of the indications for cesarean section is also quite apparent when we consider that (1) the majority of the cesarean deliveries were elective repeat sections, and (2) the major complications of pregnancy can be shown to result in but little increase in abnormal breathing, no matter what the method of delivery.

Group II breathing, in our previous publication, was considered "normal" because there was no associated mortality, but now

must be considered as perhaps not strictly normal (Table III).

It would seem that Group II breathing follows a pattern more nearly like Group III than Group I. We are not at all sure of the significance of this tendency but hope to follow it further in our continuing study.

Effect of antepartum care

We continue to have a considerable number of patients present themselves for delivery at our hospital without the benefit of prenatal care. Forty-eight of the patients with full-term vaginal deliveries, 110 of those with the "large premature" vaginal deliveries, and 46 of those with the "small premature" vaginal deliveries had no prenatal care and showed a Group III breathing rate almost double that of those patients with more adequate care. It should be stated that we have no idea at the moment what in our care program could possibly be responsible for improving the breathing pattern of the babies whose mothers have had this care.

Nevertheless, lack of prenatal care must be mentioned as a factor associated with an increased incidence of abnormal breathing.

Effect of gravidity

In comparing the breathing patterns of the babies of primigravid mothers with those of multigravidas, we found that the 210 full-term, vaginally delivered primigravidas produced babies with 9 per cent Group III breathing as contrasted with 5 per cent for the multigravidas. While the majority of these patients were under 20 years of age, we would, at the moment, discount this fact. Moreover, the premature babies of primigravid women had the same incidence of abnormal breathing in this series as did the premature babies of the multigravid mothers. Large babies (above 3,500 grams) showed an incidence of 12 per cent Group III breathing in the primigravid patients, but an almost "average" 7 per cent in the multigravid patients. The number of babies so involved, 43 of primigravidas and 159 of multigravidas, is too small a group to be conclusive. These minor differences are mentioned as being presently apparent in our material but may well disappear as the volume of material is increased.

Effect of third trimester bleeding

Vaginal bleeding of definite amount in the third trimester seems to be an important factor, regardless of the cause of this bleeding (Table IV). The total number of patients (85) is so small that sweeping conclusions cannot be drawn.

Effect of other complications of pregnancy and of anesthesia

Many of the major complications of pregnancy do not result in an increased incidence of abnormal breathing. This can be reported with regard to anemia, Rh factor influence, diabetes, and toxemia, although the number of patients in this series with either diabetes or severe toxemia is few. Neither the pre-pregnancy weight of the mother nor the weight gain during pregnancy had a high association with Group III breathing.

First stage analgesia and second stage anesthesia, as practiced by us, have shown no significant relation to abnormal breathing. We still feel, however, that regional anesthesia is safest for premature infants. In the small premature group, no analgesia and/or no anesthesia were followed by the highest incidence of Group III breathing. (Only 39 and 23 patients, respectively.) Me-

Table III. Frequency of each type of breathing expressed in percentages and related to weights of babies delivered vaginally

Weight (grams)	Group I	Group II	Group III
1,000-1,745	12	24	64
1,750-2,495	42	43	15
2,500-2,995	64	30	6
3,000-3,495	59	35	5
3,500-3,995	53	40	7
4,000 and over	28	58	14

Table IV. Relation of third trimester vaginal bleeding to frequency of Group III breathing

	Cause of bleeding unknown		Cause of bleeding known	
	No. patients	% Group III	No. patients	% Group III
Term deliveries	11	18	13	62
Large premature	28	29	12	25
Small premature	14	70	7	71

Table V. Frequency of Group III breathing in relation of duration of delay period before onset of breathing and cry

	Delay of 30 seconds		Delay of 30 seconds to 2 minutes		Delay of 2 to 5 minutes		Delay over 5 minutes	
	No. patients	% Group III	No. patients	% Group III	No. patients	% Group III	No. patients	% Group III
Full-term	771	0.5	30	7	7	43	5	20
Large premature	600	14	37	16	7	55	6	17
Small premature	137	49	13	65	6	100	9	100

dian forceps deliveries have not yet been in sufficient numbers to analyze. (One baby died immediately of intracranial hemorrhage.) Premature rupture of the membranes has not, in this series, to date resulted in a definite increase in abnormal breathing.

Effect of prolonged labor

In analyzing the factor of prolonged labor, we found that a first stage of more than 24 hours seemed to produce a definite increase in Group III breathing. There were only 30 such patients in the 813 full-term, vaginally delivered mothers, and these had an incidence of 17 per cent Group III as compared with a 6 per cent incidence for those whose first stage was 12 hours or less. The length of the second stage has had no apparent relationship to an abnormal breathing pattern in the infant.

A firm cervix also seemed to result in two to three times as much Group III breathing. That there is a definite correlation between the firm cervix and prolonged labor has been previously pointed out by the author.

Significance of delayed breathing

Exclusive of the small premature infant, delayed establishment of respiration and cry is the most important sign associated with Group III breathing (Table V). Whereas

this is true at all weight levels, the number of patients is too small to be conclusive.

Whether the delayed respiration and cry results in an increased proportion of Group III breathing or the same cause produces both is not obvious. In any event, we must try to avoid asphyxia until further information is available.

Conclusions

1. Our earlier impression that there is a high incidence of abnormal breathing in the small premature baby has been confirmed by our continuing study.

2. Other factors which have been shown to be highly associated with abnormal breathing are asphyxia, vaginal bleeding, abdominal delivery, lack of prenatal care, and prolonged first stage of labor.

3. Certain other "suspicious" factors have shown no appreciable relationship to abnormal breathing, namely, toxemia, premature rupture of the membranes, the type of analgesia and/or anesthesia, anemia, or Rh incompatibility.

4. The number of patients in this series is still inadequate finally to adjudge the effect of these complications of pregnancy.

REFERENCE

1. Calkins, L. A., and Miller, Herbert C.: *AM. J. OBST. & GYN.* 78: 1005, 1959.

Discussion

DR. ROBERT A. ROSS, Chapel Hill, North Carolina. The paper presented is a continuing study of the breathing pattern in the newborn

as observed by the authors. A previous report listed 612 premature deliveries by vagina and 189 cesarean section deliveries with 216 term

vaginal deliveries as controls. The present series brings the totals to 813 term deliveries, 800 premature deliveries, and 250 cesarean sections.

The highest newborn death rate was in those infants who had an initial rate of approximately 43 respirations per minute and whose rate at the end of 6 hours had risen to 60 and gradually fell to 51 in 24 hours. Some deaths occurred in babies who had an initial rate of 60 to 65 and whose rate fell to 45 to 55 in the first 6 hours and was maintained at 42 in 24 hours. The favorable group had an initial rate of 40 which was fairly constant during the first 24 hours of life. Of the infants who had a significant increase in respiration rate during the first day or two, half the number developed cyanosis and one quarter of them died during the first week.

In Group III infants the respiratory tidal volume was found to be lessened, although the rate showed increase. Examination of femoral blood after birth revealed lowered pH and increased CO_2 tension in many of these infants. This was thought to be due to a reduction of the alveolar space, and to the fact that these infants experienced less difficulty in oxygenating their blood satisfactorily than in maintaining acid-base balance, and that infants with respiratory insufficiency have uncompensated respiratory acidosis (H. C. M.).

The authors state that the greatest single factor influencing an abnormal pattern of breathing is prematurity. The next is delivery by cesarean section, although they do not believe that this fact is associated with the antepartum and intrapartum complications that might lead to this type of delivery. The third factor was lack of prenatal care, and the fourth, bleeding in the last trimester of pregnancy. Prolonged first stage of labor and the presence of a firm cervix also caused an increase in the incidence of abnormal breathing.

The authors emphasize that delayed establishment of respiration and cry is an important precursor of Group III breathing. They restate their conviction that major complications of pregnancy—*anemia*, *Rh factor incompatibility*, *diabetes*, and *toxemia*—do not result in an increased incidence of abnormal breathing, nor does obstetric analgesia and anesthesia as practiced by the author.

We believe that the authors now have a sufficient number of patients, but we doubt that their attempt to correlate an empiric observation such as rate of breathing as recorded by them,

to ultimate prognosis of a newborn infant is completely successful. A definite correlation of cause and effect in our opinion has not been established by the data presented. With us the type of respiration is more significant than the rate. The Apgar index is simple and reasonable and is of great value; its use might aid in correlating subsequent breathing patterns, prognosis, and morbidity. We place great dependence in the Apgar index and believe that exact information regarding prognosis can be obtained within 15 to 30 minutes by accurate interpretation and recording of the five criteria at intervals. We have found accurate count of the respiratory rate of premature infants difficult and have placed more significance on the type of respiration and visible evidence of effort.

It would be helpful to know the pH, pCO_2 , and buffer base in the Group III infants as determined from cord blood immediately on birth. A report of the findings at necropsy of specimens of brain and lung seems indicated. We know of the scrupulous recordings and of the conservative practices concerning analgesia, anesthesia, and mode of delivery of the author, but a more complete documentation in the essay would be helpful.

In a joint study of perinatal mortality, with Duke and Bowman Gray, a simple and reliable test of the probability of fetal and maternal complications in pregnancy was outlined. By grading education of the mother and the occupation of the father one can establish the socioeconomic level. Our numbers are now statistically sound and we have accurate figures regarding the instance of such maternal complications as *toxemia*, *premature rupture of membranes*, and *prematurity*. We would be interested in seeing the authors' series subjected to some such outline, which, we believe, would furnish information regarding the amount of prenatal care in patients not registered in the clinic for antenatal care.

DR. ROBERT H. BARTER, Washington, D. C.
In the work which we did with the use of hypothermia in the treatment of severe *toxemia* of pregnancy, 10 babies were delivered from 10 severely *toxemic* mothers under treatment with hypothermia. All of the infants survived. Such might not have been the result if the mothers had not had the benefits of hypothermia. The babies who were born of mothers under hypothermia had a breathing rate of only 3 respirations per minute at birth. The babies were al-

lowed to regain their normal temperatures slowly with no artificial warming. Gradually, as they regained normal body temperatures, their respiratory rates became normal. All survived. It is our experience, therefore, that the rate of breathing is perhaps not as important as the authors' paper would lead one to believe. The babies with rapid respirations might do better if subjected to hypothermia.

Recently Dr. Bjorn Westin in Sweden has done some interesting work using hypothermia and intra-arterial transfusions of oxygenated blood in the therapy of fetal depression. In the 6 cases which he reported, the respirations of the depressed infants became established as soon as the babies were adequately chilled. He lowered some of the infants' temperatures down to 23° C. No effort was made to rewarm those babies, and all but one survived.

Ideally, one should find it unnecessary to treat depressed babies, because, with excellent obstetrical care and particularly with the elimination of prolonged labors, there should be no depressed infants. Sedation can be employed adequately but judiciously.

However, when one is confronted with the unfortunate situation of the depressed infant, perhaps hypothermia and the use of oxygenated transfusions may prove to be lifesaving factors. They have not been employed in this country up to the present time, to the best of my knowledge.

DR. CALKINS (Closing). I would like to point out to Dr. Barter that we are not concerned with the rate of respiration. We are concerned with the increase in that rate as time goes on. That is what makes the baby Group III and that is what we want to find the cause of.

Connective tissue changes incident to cervical effacement

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LITTLE inquiry has been directed toward the specific changes which occur in the human cervix to permit effacement and consequent dilatation without injury. It is well known that the nonpregnant cervix is rigid, that it can be dilated only by much force, and that this forcible dilatation may be accompanied by injury or tearing. During pregnancy the cervix becomes softer, but it still cannot be dilated easily except in the event of miscarriage or the onset of labor. In the former case it dilates prior to the passage of any tissue, such that a large Hegar dilator can be introduced with ease; in the latter case it may remain rigid in early labor such that forcible dilatation is impossible. As labor progresses it becomes softer and thinner and dilates without injury to permit the passage of the head. Within a week of delivery, a portion of its old rigidity has returned, and within a month there is little evidence of this dramatic series of events. It is curious that so little effort has been made to explain these phenomena.

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In 1947, evidence was presented to show that the basic structure of the human cervix is connective tissue.¹ This finding was confirmed,² and was later reaffirmed³ following a difference of opinion which resulted at least in part from semantics and partially from the misinterpretation of apparently opposing data. Possibly the resulting confusion was akin to the differing concepts of the elephant according to whether the tail, the ear, the flank, or the leg was examined. In any event, the evidence now available permits the conclusion that, although the cervix does contain muscle⁴ whose activity can be recorded,⁵ nevertheless, the major portion of the substance of the cervix is connective tissue. Moreover, it seems clear that it is this connective tissue quality which imparts to the cervix its various reactions and roles which are so different from those of the muscular corpus.^{6, 7} Accordingly, the changes in the cervix during pregnancy and labor must be explained in terms of the reactions, not of muscle, but rather of connective tissue.⁸

The ultimate solution of the problem of cervical effacement will require that one establish, first, the fact that changes actually do occur in the cervical connective tissue. The exact nature of the changes, and their interrelationships, should then be documented. Finally, the mechanism by which they are produced must be determined. It was with these thoughts in mind that the present studies, which represent only the

first and most superficial probes, were made.

The work we wish to present here consists of two parts: (1) an evaluation of certain structural changes in the fibrillar elements of the cervical connective tissue in conjunction with pregnancy and labor, and (2) an effort to detect certain concurrent chemical changes as evidence of connective tissue alteration.

Materials

If it is correct that the process of effacement is dependent upon a change in the character of the connective tissue, the exact end point of this change should occur at the moment the cervix has reached full dilatation, and the opposite extreme should be found in the cervix of nonpregnant women of childbearing age. The control nonpregnant specimens, in the age group of 32 to 40 years, were not difficult to obtain; but obtaining adequate cervical tissue at the moment of complete dilatation is not clinically feasible. Accordingly, as a substitute, wedge biopsy specimens 3 cm. in length and approximately 2 cm. wide at the base were removed from the posterior lip of the cervix immediately after delivery in 10 patients. One half of the tissue was fixed immediately in Bouin's solution for microscopic study (1), and the remainder used for chemical analysis (2). In addition to this material, the cervixes from 10 cesarean hysterectomy specimens obtained prior to labor were available for microscopic study.

Methods and results

1. *The fibrillar elements.* From the histologist's standpoint, the fibrillar elements of connective tissue include the elastic fibers, the collagenous fibers, and the reticulum. The first, elastic fibers, can be eliminated at the outset, since our repeated efforts to demonstrate them in significant amount (by orcein and resorcinofuchsin) have been unsuccessful. The only elastic fibers of significance which we could find were in and about the walls of the larger blood vessels.

A. *The collagenous fibers.* These fibers, the principal fibrillary component of con-

nective tissue, were demonstrated by Milligan's trichrome stain⁹ and also by examination of stained and unstained sections using polarized light.

In the nonpregnant cervix, the distribution of collagenous tissue, as previously demonstrated by examination with the scanning objective of the light microscope, was reaffirmed. With Milligan's trichrome stain, the bulk of the cervix stains intensely green, and the corpus, purple. The cervical collagenous fibers, under high power, appear as tightly woven bundles of interlacing bright green fibers. Each fiber consists of many parallel fibrils which are held together by a cementing substance.¹⁰ The individual fibrils cannot always be defined clearly, since their diameters approach the limit of the resolving power of the light microscope.

Under polarized light, the collagenous fibers can be distinguished clearly by reason of their birefringence.^{10, 11} In some areas of smooth muscle, portions of the field may transmit light as the result of reflection from the collagen surrounding the individual muscle fibers. The myofibrils of smooth muscle are also doubly refractile, but are very fine and can be readily distinguished from the bright, luminiferous glow of the collagen bundles. Collagen is also identified in the corpus by means of polarized light, but its distribution is quite different since here the collagen is interspersed between the muscle cells and appears to act principally in a supporting role. In most cases the transition from basically fibrous cervix to basically muscular corpus is abrupt, occurring over the course of only a few millimeters.

In the cervix in late pregnancy (cesarean hysterectomy specimens), edema is quite pronounced, as evidenced by many clear spaces between the individual collagen fibers. In addition, the fiber diameters are slightly increased and the central portions stain less intensely.

In the cervix immediately after delivery, edema is a prominent feature, but interstitial hemorrhage is surprisingly rare. Also, inexplicably, in the postpartum specimens the vascularity is greatly increased. In addition,

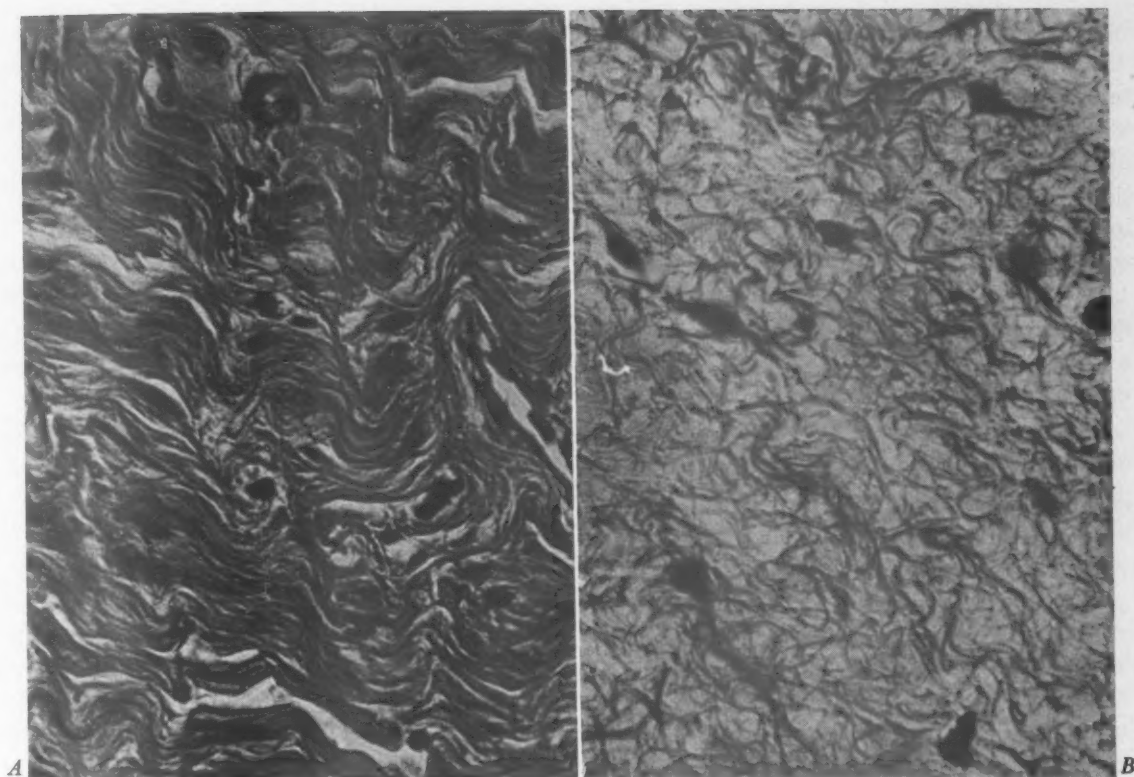


Fig. 1. Cervix, midportion, approximately 1 cm. above plane of external os. (Milligan's trichrome stain for collagen.) *A*, Nonpregnant. *B*, Immediately post partum. Dissociation of fibers and increased tissue fluid are evident in *B*. ($\times 835$.)

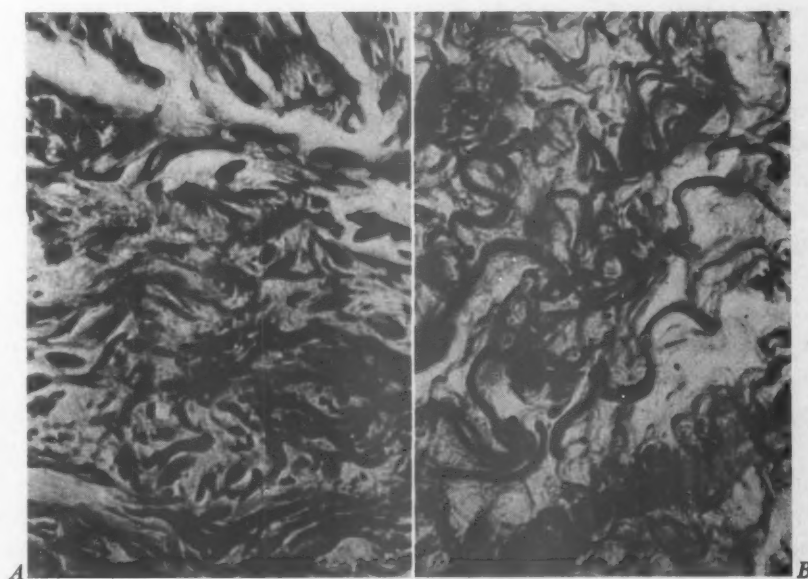


Fig. 2. Reticulum (Wilder's silver impregnation). Same sites as in Fig. 1. *A*, Nonpregnant. *B*, Pregnant at term. ($\times 1,200$.)

the collagen fibers show what appears to be a dissociation into their fibrillar components, since the fibers in these specimens run in varying directions and give off branching offshoots which are of lesser diameter than the major trunk. In some areas the branching is sufficiently complex to suggest an entirely random orientation of the fibers (Fig. 1). Collagen fibers in the nonpregnant cervix do branch, but they are more stout, and branching is a less prominent feature since the fibers tend to run parallel to one another.

These changes were presumed not to have resulted from the trauma of labor, since nonpregnant cervixes subjected to the most violent mastication in the colloid mill failed to show the fiber dissociation described here.

B. The reticular fibers. These were demonstrated by the Wilder silver impregnation method,¹² which stains them intensely black. According to classical concepts, these fibers are very fine, highly branched, threadlike structures which form a network in and around the bundles of collagenous fibers and around the smooth muscle cells. In the nonpregnant cervix, the reticular fibers appear as short segments, very irregularly dispersed or clumped in haphazard relation to the collagen bundles. In the pregnant cervixes (cesarean hysterectomy) reticular fibers are more robust and in general more luxuriant. In addition to being stouter, they can be traced in their wavelike branching course which more frequently tends to parallel the collagen fibers. This difference in reticulum is very characteristic and by this means alone it is possible to distinguish the pregnant from the nonpregnant cervix (Fig. 2).

In the cervix immediately after delivery, the structure of the reticular fibers appears to be much the same as in the cervix at term, except that they are more widely separated and somewhat thinner.

2. The chemical changes. For practical purposes, collagen is uniquely characterized by the presence of hydroxyproline. Minute amounts of this amino acid have been reported in elastin, but with this possible exception hydroxyproline occurs only in collagen.¹³ Hence, its presence in significant

Table I

	<i>Nonpregnant (ages 32-40)</i>	<i>Immediately post partum</i>
No. of cases	32	10
% Hydroxyproline	10.2 \pm 1.76*	4.7 \pm 1.54*

*Standard deviation.

amount gives unequivocal evidence of the presence of collagen; its concentration may provide an approximation of the amount of collagen.

Employing the tissues mentioned above, the epithelial elements were trimmed away, and the remainder analyzed for hydroxyproline by the method of Neuman and Logan¹⁴ as modified by Martin and Axelrod.¹⁵ The accuracy of the method is from 1 to 2 per cent. In order to test the method in our hands, and prior to the testing of any cervical tissues, (a) standard rat tail tendon analyses were made to compare with published figures; (b) the trichloroacetic acid residue was tested by paper chromatography to test the completeness of extraction; (c) hydroxyproline standard added to the trichloroacetic extract was recovered quantitatively; and (d) tissue determinations were done in duplicate. The results of these checks were satisfactory.

Hydroxyproline was recorded as the percentage of the dry weight. The findings are shown in Table I.

Although the difference between the two series is statistically significant, no information is provided as to the time of onset of the drop in hydroxyproline concentration.

Comment

The softening and increasing dilatability of the cervix during pregnancy have been documented in the human being¹⁶ and in the rat.⁷ In the rat, the important studies of the Harknesses⁷ have done much, not only to establish the changes which occur, but, of especial importance, to assist in their explanation. These workers have found that during the last half of pregnancy the stretchability of the cervix increases progressively. They have found further that most of the

resistance to stretch is provided by the connective tissue framework. Concomitant with the increasing stretchability is a gradual, if slight, decline in the concentration of collagen. Accompanying this, a relative increase in hexosamine was noted. Although hexosamine may be found in other areas as, for example, plasma proteins, it has been used to give an approximation of the concentration of mucopolysaccharide and, hence, to give some indication of the proportion of ground substance present. It is presumed that it is one or another component of the ground substance (possibly the protein complex of chondroitin sulfate) which "cements" the collagen fibrils together.¹⁷ The Harknesses have suggested that since the gestational changes in the mouse cervix and the mouse symphysis, as outlined by Steinetz and associates,¹⁸ not only parallel one another in time but also in the local tissue effect, the hormone relaxin may be responsible for both. Although a detailed discussion of relaxin is not pertinent to this paper, it is of interest that the primary effect of relaxin upon the connective tissue of the mouse symphysis is to cause a loosening or splitting apart, rather than a dissolution, of the fibrillar elements of the collagen,¹⁹ a change which is strikingly similar to that which we have described here. Also, Hughesdon²⁰ has remarked upon the evident ability of the theca interna cells of the ovary to produce "loosening" of the surrounding tissue in anticipation of ovulation, and he postulates that relaxin may be concerned in this. With regard to the cervical softening which occurs in pregnancy, he suggests²¹ that the process may be equivalent and that dissociation of the fibers, rather than dissolution, may be the significant factor.

Since reticulum is regarded by some as young or "pre-" collagen, the observed changes in these fibers must be given significance in the total connective tissue picture. The more robust, orderly appearance of the reticular networks suggests proliferation and growth which is most marked immediately before labor and is essentially un-

changed following labor. Also, the loosening of the networks is striking. With regard to the collagenous fibers, interstitial edema in late pregnancy and evident loosening of the individual fibrils was remarked upon by Stieve.²² After the completion of effacement and dilatation, our finding of excessive branching and more delicate nature of the fibers confirms the likelihood of fiber dissociation, which was mentioned above, and supports the notion that the cementing substance between the fibrils has been altered.

The significant decline in the concentration of hydroxyproline per unit of dry tissue may be interpreted as representing a drop in the concentration of collagen. Although it is possible that there may be an actual loss, or dissolution, of collagen, it is also possible, and perhaps more consistent with current thinking, to presume that the percentage decline in hydroxyproline reflects a proportionate increase in the ground substance, probably accompanied by a change in its composition. In this connection, Gillman and Pillay²³ have recently reported an increase in serum mucopolysaccharides during pregnancy and a further sharp rise in the 24 hours after labor. Evidence is also presented of profound gestational changes in the ground substance of arteries and of dermal connective tissue. They did not study the cervix, but it is likely that changes here might be even more dramatic.

This work is presented as a preliminary investigation of a problem, the ultimate solution of which will be of signal importance to obstetrical practice. More penetrating inquiry must now be made of the specific changes which occur in both formed elements and ground substance of the human cervix and of their timing with relation to the stages of pregnancy, labor, and the puerperium. Although the field of connective tissue metabolism is a forbidding one whose darkest secrets are disclosed only to the initiated, we are nevertheless convinced that the explanation for cervical effacement must be sought here. If those whose primary interest and knowledge is connective tissue were to turn their thoughts to the cervix,

renouncing such ordinary pursuits as coronary disease and atherosclerosis, the problem would be solved much sooner.

Conclusions

1. The basic structure of the human cervix is connective tissue, and the outstanding component of this is collagen.

2. During pregnancy and prior to labor, the collagen fibers appear to be swollen and enlarged, but the integrity of the fiber bundles is not otherwise changed. At the conclusion of labor the collagen fibers are smaller and very highly branched, and they give the impression of dissociation of the component fibrils one from another.

3. The reticulum prior to labor is more luxuriant than in the nonpregnant cervix, and the continuity of the fibers is much more easily traced. The diameters of the fibers are slightly increased, and the networks more easily defined. After labor, the reticular networks show little change from their orientation and form prior to labor.

4. The hydroxyproline percentage of the dry weight is significantly less in the cervix immediately after delivery than in the cervix in the nonpregnant individual. This evidences a decline in the concentration of collagen.

5. It is postulated that the physiologic functions and physical properties of the cervix in the various conditions of nonpregnancy, pregnancy, and labor are determined especially by the reactions and status of the connective tissue framework.

6. It is suggested that the fundamental changes may concern the ground substance rather than the collagen itself, and that consequent dissociation, and not dissolution, of the fibers is the change which permits effacement and dilatation.

We are indebted to Miss Mildred Milligan, who carried out the special stains, and to Mrs. Mary Pawl, who did most of the chemical determinations. Also, particular mention should be made of the monographs and symposia²⁴⁻³⁰ which have been so helpful to us in our approach to this problem.

REFERENCES

1. Danforth, D. N.: *AM. J. OBST. & GYNEC.* 53: 541, 1947.
2. Schwarz, O., and Woolf, R. B.: *AM. J. OBST. & GYNEC.* 55: 151, 1948.
3. Danforth, D. N.: *AM. J. OBST. & GYNEC.* 68: 1261, 1954.
4. Hughesdon, P. E.: *J. Obst. & Gynaec. Brit. Emp.* 59: 763, 1952.
5. Nixon, W. C. W.: *AM. J. OBST. & GYNEC.* 62: 964, 1951.
6. Danforth, D. N.: *Clin. Obst. & Gynec.* 2: 45, 1959.
7. Harkness, M. L. R., and Harkness, R. D.: *J. Physiol.* 148: 524, 1959.
8. Danforth, D. N.: *Clin. Obst. & Gynec.* 2: 248, 1959.
9. Milligan, M.: *Am. J. Clin. Path.* 10: 184, 1946.
10. Maximow, A. A., and Bloom, W.: *A Textbook of Histology*, ed. 7, Philadelphia, 1957, W. B. Saunders Company, p. 63.
11. Gustavson, K. H.: *The Chemistry and Reactivity of Collagen*, New York, 1956, Academic Press, Inc., p. 71.
12. Wilder, H. C.: *Am. J. Path.* 11: 817, 1935.
13. Jackson, D. S.: In Page, I. H., editor: *Proceedings of a Conference on Connective Tissue, Thrombosis, and Atherosclerosis*, New York, 1959, Academic Press, Inc., p. 67.
14. Neuman, R. E., and Logan, M. A.: *J. Biol. Chem.* 186: 549, 1950.
15. Martin, C. J., and Axelrod, A. E.: *Proc. Soc. Exper. Biol. & Med.* 43: 461, 1953.
16. Halliday, E. C., Jacobs, G. V. W., and Heyns, O. S.: *J. Obst. & Gynaec. Brit. Emp.* 65: 409, 1958.
17. Meyer, K., Hoffman, P., and Linker, A.: In Page, I. H., editor: *Proceedings of a Conference on Connective Tissue, Thrombosis, and Atherosclerosis*, New York, 1959, Academic Press, Inc., p. 181.
18. Steinetz, B. G., Beach, V. L., and Kroc, R. L.: *Endocrinology* 61: 271, 1957.
19. Storey, E.: *J. Path. & Bact.* 74: 147, 1957.
20. Hughesdon, P. E.: *J. Obst. & Gynaec. Brit. Emp.* 65: 707, 1958.
21. Hughesdon, P. E.: Personal communication, 1960.
22. Stieve, H.: *Ztschr. mikr.-anat. Forsch.* 11: 291, 1927.
23. Gillman, T., and Pillay, R. A.: *Surg. Gynec. & Obst.* 109: 709, 1959.
24. Asboe-Hansen, G., editor: *Connective Tissue in Health and Disease*, Copenhagen, 1954, Ejnar Munksgaard.
25. Gustavson, K. H.: *The Chemistry and Reactivity of Collagen*, New York, 1956, Academic Press, Inc.
26. Page, I. H., editor: *Proceedings of a Con-*

- ference on Connective Tissue, Thrombosis, and Atherosclerosis, New York, 1959, Academic Press, Inc.
27. Pearse, A. G. E.: *Histochemistry, Theoretical and Applied*, ed. 2, Boston, 1960, Little Brown & Company, chap. 7.
28. Ragan, C., editor: *Transactions of the Josiah Macy, Jr., Foundation Conferences on Connective Tissue*, New York, 1950-1954, Josiah Macy, Jr., Foundation.
29. *Symposia of the Society for Experimental Biology*, Number IX: *Fibrous Proteins and Their Biological Significance*, New York, 1955, Academic Press, Inc.
30. Turnbridge, R. E., editor: *Connective Tissue—A Symposium Organized by the Council for International Organizations of Medical Sciences*, Oxford, England, 1957, Blackwell Scientific Publications.

Discussion

DR. H. CLOSE HESSELTINE, Chicago, Illinois. Drs. Danforth, Buckingham, and Roddick have presented their evidence and their views on their observations on the structure and physiological behavior of the cervix in pregnancy and labor. Perhaps not totally unrelated to this study are facts about the mechanism and changes in contraction and relaxation of muscle (the structure as a unit or as individual cells). There must be changes also in the dermal layers and other tissues where changes occur repeatedly and rapidly. One may ask what was done to make sure that the contents of cells of cervixes remained unchanged after death of the tissue.

The uterus and the cervix go through considerable if not enormous changes. The cervix by dilatation alone has its diameter increased some 10 times (plus or minus). This requires even a greater change in circumference. There are few organs of the body that exhibit this faculty of great change in a short span of time. When one considers the degree of resistance or rigidity of the cervix persistent throughout most of the pregnancy, one must be convinced that with effacement and dilatation a near miraculous situation has occurred. Furthermore, the relative infrequency of damage to the cervix emphasizes the physiological propensities of this organ.

Dr. Danforth and his colleagues have documented their paper with illustrations and close it with 6 specific points. One might ask for an explanation of the mechanism of the changes in connective tissue of the cervix from a relatively inelastic, rigid tissue to one of a dilatable nature. One's concept of connective tissue may vary in relation to the tissue which one uses for comparison or correlation.

I trust that Dr. Danforth and his colleagues pursue this whole matter further. When we understand how and why the cervix behaves as it does, we should be able to apply this knowledge for benefit to our patients. All efforts which

increase our comprehension of physiological behavior reduce at the same time our theories to facts. The value of a contribution may not be fully appreciated at the time of its introduction.

DR. CARL P. HUBER, Indianapolis, Indiana. For years there has been controversy concerning the actual existence of what is spoken of as cervical dystocia. There have been those who felt it was real and represented a rigid, undilatable cervix, and there have been others who felt that most cases of apparent cervical dystocia were actually examples of inadequate uterine contractions. This paper points to a way to demonstrate lack of changes in the cervix that fails to respond to uterine contractions. It perhaps points a way to the explanation for what we call a ripe cervix, and it may offer a means by which we can determine the physiological maturity of the cervix.

DR. DANFORTH (Closing). This is but a preliminary study, designed to demonstrate some of the changes which do occur. I hope that some of the investigators who are concerned with connective tissue will interest themselves in this, for the field is unbelievably abstruse for the uninitiated. We will continue to work with it, and I think we shall make some headway, but it will not be rapid. We have now in progress some electron microscopy studies, some other work with special stains, and some other chemical studies on which we are not now prepared to report. We are hopeful that some of these will clarify the problem.

Dr. Hesseltine mentioned the degenerative changes occurring between the time of removal and the time of examination of the prepared tissues. This same criticism can be made of any histological work, for the moment you interfere with the blood supply degenerative changes begin. The best we can do is to process the tissue instantly when it becomes available, and this we have done.

Refractory anemias of pregnancy

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PREGNANCY may be complicated by anemia which fails to respond to specific therapy with any of the presently known hematinics. Fortunately their occurrence in a form severe enough to produce an obstetric problem is limited. Continued investigations on these nonresponsive anemias have demonstrated that they are a heterogeneous group of varied etiology. Within this group, four types of anemia are encountered most frequently, namely, the hemoglobinopathies such as S-S, S-C, and C-C disease, familial and acquired hemolytic anemia, the anemia of infection, and a refractory anemia of unknown etiology. This report will consider only the anemia of infection and refractory anemia of pregnancy. Data will be presented from which diagnostic criteria and the clinical course of these two entities can be established.

Terminology

Hematologic terminology can be confusing, for in the broad meaning of the term a refractory anemia is one which does not respond to specific treatment. In the parlance of the hematologist, however, the term "refractory anemia" is used more precisely to designate an anemia which is often associated with granulocytopenia and thrombocytopenia, is not associated with chronic renal, hepatic, or malignant disease, and is refractory to all treatment ex-

cept transfusions of whole blood. Synonyms for refractory anemia include aregeneratory, hypoplastic, aplastic, and myelophthisic anemia. I used the term "hypoplastic anemia" in a previous publication to describe a transient and refractory anemia of pregnancy.¹ This was done because the bone marrow in each case was hypoplastic. Further study has shown that a correlation between bone marrow function and morphology is not always possible. In addition, reports of aplastic anemia associated with pregnancy have been documented in the literature.²⁻¹¹ For these reasons it is preferable to employ the more inclusive designation of refractory anemia of pregnancy.

Methods

All of the patients who comprise this study were registered in the clinics of the University of Nebraska or Minnesota. Data on 15 patients are to be presented, 2 with anemia of infection and 13 with refractory anemia. Determinations for the hemoglobin, packed cell volume, reticulocytes, leukocytes, platelets, and serum iron were carried out in the departmental research laboratory by methods previously described.¹² Normal values during pregnancy have been reported.¹² Other procedures performed to exclude a hemolytic process or a hemoglobinopathy were done by the University Hospital laboratory. These tests include the determination of the bilirubin, urine and fecal urobilinogen, red cell fragility, plasma hemoglobin, sickle cell preparation, and the electrophoretic pattern. In none of the patients who comprise this report was there evidence for either a hemolytic disease or a hemoglobin abnormality.

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The bone marrow biopsy specimens were obtained from the sternum by means of a University of Illinois needle. The aspirated marrow fluid was transferred to a glass plate and the particulate matter removed. Smears were made directly from the marrow aspirate or from the myeloid-erythroid layer after centrifugation. Wright stain was used to prepare the smears for microscopic examination. Differential counts were based on at least 500 cells. The particulate matter was crushed and smeared separately and stained for iron with 20 per cent potassium ferrocyanide. To describe bone marrow morphology, the Downey classification of cell types has been used. Data obtained from bone marrow biopsies on 26 healthy women obtained at different stages of pregnancy form the basis for the differential counts and the morphologic description of the normal bone marrow in pregnancy.¹³

Case reports

Brief abstracts and hematologic data of 4 case histories are provided to illustrate the important features of pregnancy complicated by an anemia of infection and refractory anemia.

Case 1 (UNH 12646). G. D., a 22-year-old para 4-0-0-3, was hospitalized on Jan. 30, 1958, for treatment of a recurrent urinary tract infection. The last menstrual period was Nov. 14, 1957. The presenting symptoms were flank tenderness, dysuria, chills, and fever. The temperature was 104° F. The urine was loaded with pus cells and cultured *Escherichia coli*. Treatment with tetracycline was effective and the patient was discharged on Feb. 5, 1958. The subsequent pregnancy and delivery in August were uneventful.

The diagnosis of anemia of infection was established by the low serum iron, the leukocytosis, toxic granulopoiesis, and a storage iron estimate of +2. Hemoglobin level on admission was 9.4 Gm. per cent. Two months prior to hospital admission a hemoglobin level of 12.7 Gm. per cent had been recorded. Significantly, she had received oral iron for the 6 months' period immediately preceding hospitalization. Complete hematologic data for this pregnancy are shown in Table I.

Without iron medication, which was purposely withheld, the patient mobilized iron reserves and synthesized sufficient hemoglobin to restore a normal hemoglobin concentration by the time of delivery. At term, all storage iron had been depleted. Five hundred milligrams of intramuscular iron was given after delivery. Hematologic values 2 months after delivery were normal.

Case 2 (UNH 6938). S. D., a 16-year-old para 0-0-0-0, was admitted to the hospital on Nov. 25, 1957, for treatment of a urinary tract infection. The estimated date of confinement was March 11, 1958. The symptoms were flank pain, chills, and fever. The temperature was 104.2° F. From her history it was apparent that she had been ill for at least a month. The urine contained numerous pus cells and cultured *E. coli*. On Gantrisin* and tetracycline the infection was cleared and she was discharged on Dec. 12, 1957. She was not seen again until the admission for delivery on Feb. 14, 1958.

The diagnosis of anemia of infection was established by the low serum iron level, the leukocytosis, toxic granulopoiesis, and a storage iron estimate of +1. At a prenatal visit 2 months prior to hospital admission, a hemoglobin level of 9.6 Gm. per cent had been recorded. She had been placed on oral iron. When she was admitted for treatment of the urinary tract infection this medication was withdrawn purposely and she received no further iron during the pregnancy. At the time of delivery she was given 500 mg. of intramuscular iron but did not return for further treatment. Complete hematologic data for this pregnancy are shown in Table II. Without iron therapy the patient made a partial hematologic recovery. All of the storage iron was mobilized, but it was not sufficient to completely restore a normal hemoglobin concentration. The patient refused to cooperate further. She was still moderately anemic at the last clinic visit and should have received additional iron therapy.

Case 3 (UNH 41670). R. K., a 28-year-old para 2-0-0-2, was referred for investigation because of severe anemia which in this and in previous pregnancies proved to be refractory to oral and parenteral iron, folic acid, crude liver extract, and vitamin B₁₂. She was admitted to the hospital for the original study on Feb. 21,

*3, 4-dimethyl-5 sulfanilamido-isoxazole, Roche Laboratories, Nutley, New Jersey.

1952. Hemoglobin level on admission was 6.7 Gm. per cent. In two previous pregnancies she had received 9 units of whole blood for correction of the anemia which had resisted all therapy. A hemoglobin concentration of 11.7 Gm. per cent had been recorded in the interval between the second and this third pregnancy. The diagnosis of refractory anemia was established on the basis of the proved refractoriness to treatment, the elevated serum iron level, the low platelet count, and a bone marrow biopsy which revealed normoblastic hypoplasia.

She was delivered uneventfully on May 2, 1952. Transfusions were withheld during this pregnancy so as to not interfere with the hematologic evaluation. Complete hematologic data during this pregnancy are shown in Table III. All therapy proved to be valueless during the pregnancy. The initial hemoglobin level was 6.7 Gm. per cent. The same value was recorded on April 20, about 12 days prior to delivery. After delivery the hematologic values slowly returned to normal. The hemoglobin level was 11.1 Gm. per cent on July 11, 1952.

Table I. Anemia of infection complicating pregnancy (Case 1)

Date	Hemoglobin (Gm. %)	Packed cell volume (%)	Reticulocytes (%)	Serum iron (gamma %)	Platelets	White blood cells	Marrow iron
11/27/57	12.7						
1/30/58	9.4	31	0.4	20	230,000	15,000	+2
2/ 5/58	10.7	35	2.6			9,700	
3/18/58	12.3	39	1.2	28			trace
6/27/58	12.8	41	0.8	60			0
8/ 1/58	12.7	41	1.1	50			
8/23/58	Delivery						
10/ 8/58	13.8	45	1.0	76			

Table II. Anemia of infection complicating pregnancy (Case 2)

Date	Hemoglobin (Gm. %)	Packed cell volume (%)	Reticulocytes (%)	Serum iron (gamma %)	Platelets	White blood cells	Marrow iron
9/18/57	9.6						
11/25/57	6.4	24	0.6	20	270,000	15,500	+1
2/14/58	9.7	33	1.5	20		10,100	0
2/14/58	Delivery						
4/11/58	10.5	37					

Table III. Refractory anemia of pregnancy (Case 3)

Date	Hemoglobin (Gm. %)	Packed cell volume (%)	Reticulocytes (%)	Serum iron (gamma %)	Platelets	White blood cells
2/21/52	6.7	23	0.8	188	151,000	7,800
3/ 4/52	6.5	21	1.0	210	130,000	
4/20/52	6.7	22	0.8	190		
5/ 2/52	Delivery					
7/11/52	11.1	36	1.6	140	285,000	

Table IV. Refractory anemia of pregnancy (Case 4)

Date	Hemoglobin (Gm. %)	Packed cell volume (%)	Reticulocytes (%)	Serum iron (gamma %)	Platelets	White blood cells	Marrow iron
6/ 5/57	8.6	28	0.7	140	130,000	10,800	+1
7/12/57	8.6	29	1.3				
8/ 9/57	8.6	28	0.9		121,000		
8/27/57	Delivery						
11/25/57	10.8	34	1.2	86	270,000	9,100	trace

Case 4 (UNH 11455). B. M., a 21-year-old para 2-0-1-2, was admitted to the hospital for investigation of an anemia which had not responded to intramuscular iron, vitamin B₁₂, and folic acid. She was admitted on June 5, 1957, in the seventh month of pregnancy. Subsequently she delivered on Aug. 27, 1957, without complication. During two previous pregnancies a similar refractory anemia had been encountered for which multiple whole blood transfusions had been given. In the interval between pregnancies, hemoglobin values of 12.7 and 12.3 Gm. per cent were recorded. The diagnosis of refractory anemia was established by the refractoriness to therapy, the normal serum iron level, low platelet level, and the presence of storage iron. The bone marrow was hypercellular with no apparent depression of normoblastic elements.

Complete hematologic data during the pregnancy are shown in Table IV. Over a 2 month period the hemoglobin concentration did not improve. She was admitted to the hospital shortly before the delivery date and given 2 units of whole blood. The postpartum hemoglobin level was 10.8 Gm. per cent. In a more recent pregnancy moderate refractory anemia recurred.

Bone marrow morphology

1. Normal bone marrow. Two aspects of any bone marrow, morphology and cell numbers, are of importance in its description and interpretation. A normal marrow contains leukocyte and erythrocyte precursors, lymphoid elements, and megakaryocytes. Their relative frequency is shown in Table V which represents a tabulation prepared from reports by 19 investigators.¹⁴

The usual ratio between white cell precursors and normoblasts is approximately 3.5 to 1. In the leukocyte series all gradations from the primitive leukoblast to the mature neutrophil, eosinophil, and basophil are seen. The slightly smaller normoblasts or erythrocyte precursors stem from a primitive myeloblast and develop into the reticulocyte, the cell which enters the peripheral circulation. During this maturation process the nuclear chromatin becomes denser and eventually the pyknotic nucleus is cast off. The cytoplasm, at first blue, takes on a

Table V. Normal bone marrow differential cell counts

	Nonpregnant (%)	Pregnancy (%)
Normoblasts	19.5	18.1
Neutrophils	65.0	70.4
Eosinophils	3.0	2.1
Basophils	0.5	0.4
Lymphoid cells	12.0	9.0

pinkish hue as hemoglobin is added. Lymphoid elements include plasma cells, macrophages, and lymphocytes. The megakaryocyte is the largest cell in which the cytoplasm disintegrates to form platelets. Illustrations of the various cell types can be found in any standard hematology text.

Aside from its function as the organ of blood cell production, the bone marrow also serves as one site of iron storage. The microscopic examination of the bone marrow matrix provides the only means of demonstrating and estimating storage iron from a readily accessible storage site. The iron is easy to recognize if the smear is stained with potassium ferrocyanide, for it takes on a blue color. The iron is enmeshed in the bone marrow reticulum or is contained within phagocytes. The quantitative estimate of storage iron is based on experience gained from the examination of normal men and women and those with varying degrees of iron excess or depletion. A +2 designation represents normal iron stores. Reduced storage iron is indicated by +1, trace, or absent.

2. Bone marrow in pregnancy. The bone marrow in pregnancy is slightly hypercellular. There is little to distinguish this marrow morphologically from marrow obtained in the nonpregnant state. The number of megakaryocytes is increased. The normoblast and leukocyte series appear normal in all respects. The relative frequency of the different cell types is not significantly altered. Included in Table V are the mean values for differential cell counts obtained during pregnancy. Variable quantities of stainable iron can be demonstrated. Investi-

gations have shown that the majority of women have partially or completely depleted iron reserves.¹⁵ This is equally true for pregnant women. Comparison of storage iron estimates early and late in pregnancy reveals a withdrawal of this available iron to meet the demands of pregnancy. These data have previously been reported.¹⁶

3. Bone marrow in the anemia of infection associated with pregnancy. Bone marrow biopsy specimens were obtained on 2 patients with chronic urinary tract infection and anemia refractory to iron medication. Both patients were pregnant. The marrows were hypercellular largely because of increased granulopoiesis. In the leukocyte series there was a marked shift to the right. Toxic granules were prominent in many of the developing neutrophils. Plasma cells were increased. Although all cells in the normoblast series were morphologically normal they were reduced relatively in number. Leukocyte to normoblast ratios were 8:1 and 5:1 in these two bone marrow biopsy specimens. The storage iron estimates were +1 and +2.

Follow-up biopsy specimens were obtained from each patient later in pregnancy and after the infection had been treated. Toxic granulopoiesis had disappeared. In association with progressive hemoglobin synthesis, erythropoiesis was active. In contrast with the original biopsy findings, stainable iron was absent in each of the predelivery biopsy specimens, for the storage pools had

been mobilized to provide the iron necessary for hemoglobin synthesis.

4. Bone marrow in refractory anemia of pregnancy. Biopsy specimens were obtained on 13 patients who were classified as having refractory anemia. Two different marrow patterns were found, a hypocellular marrow with reduced erythropoiesis and a hypercellular marrow with active erythropoiesis. There were 11 of the first type, 2 of the second. In the hypocellular marrow the predominant change was the relative and absolute reduction in normoblasts. The percentage of normoblasts varied from 5.4 to 14.6 per cent compared with normal values of 18 to 22 per cent. The normoblasts were morphologically normal. Granulopoiesis was relatively increased. As a variant two marrow specimens from patients who by all other criteria must be judged as having refractory anemia were hypercellular with relative increases in normoblasts. Again the morphologic picture of the normoblasts was normal. Megakaryocytes were increased in all the marrow specimens of this group. Iron storage estimates were done on 5 of the 13, and in all 5 iron was seen ranging from a trace to +2. These data are shown in Table VI.

5. Hematologic data for anemia of infection and refractory anemia of pregnancy. Determinations for the hemoglobin concentration, packed cell volume, reticulocytes, serum iron, platelets, and leukocytes were obtained as a part of the initial evalu-

Table VI. Refractory anemia of pregnancy (bone marrow differential cell counts)

Patient	Normoblasts (%)	Neutrophils (%)	Eosinophils (%)	Basophils (%)	Lymphoid cells (%)	Marrow iron
M. A.	13.9	69.6	3.1	0.4	13.0	Trace
P. B.	11.2	76.4	2.2	0.0	10.2	+2
E. S.	5.4	84.4	1.8	0.6	7.8	—
M. R.	13.7	70.0	0.4	0.6	15.3	—
M. L.	14.6	75.0	2.0	0.6	7.8	—
M. B.	14.0	71.4	2.2	1.0	12.4	—
V. W.	10.2	79.2	0.6	0.4	9.2	—
H. F.	12.8	77.6	1.0	0.2	7.4	—
H. F.	10.2	77.4	2.4	0.4	9.6	—
J. J.	14.2	75.8	1.0	0.4	8.6	+1
R. K.	9.0	71.0	5.7	2.0	12.3	—
A. Y.	26.1	59.7	2.8	0.2	11.2	Trace
B. M.	31.0	53.8	4.0	0.6	10.6	+1

Table VII. Hematologic data for refractory anemia of pregnancy and the anemia of infection

Patient	Hemoglobin (Gm. %)	Packed cell volume (%)	Reticulocytes (%)	Serum iron (gamma %)	Platelets	White blood cells
<i>Anemia of infection</i>						
G. D.	9.4	31	0.4	20	230,000	15,000
S. D.	6.4	24	0.6	20	270,000	15,500
<i>Refractory anemia</i>						
B. M.	8.6	28	0.7	140	130,000	10,800
M. A.	9.7	30	1.1	97	112,000	7,700
J. J.	9.1	29	0.2	127	162,000	7,100
P. B.	8.8	32	0.6	170	122,000	6,400
A. Y.	9.1	33	1.0	128	140,000	5,200
E. S.	8.6	27	1.2	—	116,000	6,750
M. R.	9.4	29	0.8	126	314,000	8,850
M. L.	8.9	30	0.6	—	—	6,500
M. B.	9.0	31	1.3	—	—	—
V. W.	9.9	32	1.2	171	—	—
H. F.	9.0	28	1.6	—	—	—
H. F.	9.9	31	1.5	141	—	—
R. K.	6.7	23	0.8	188	151,000	7,800

ation on each patient. These data are shown in Table VII.

Criteria for diagnosis

1. Anemia of infection. In many respects the anemia of infection resembles iron deficiency anemia. The peripheral blood picture in the two types is quite similar. The erythrocytes are small and hypochromic. In both, the serum iron is low and platelets are normal. The leukocytosis associated with chronic infection may be more than usual for pregnancy. In other important respects the anemia of infection differs from iron deficiency anemia. In the bone marrow the most significant diagnostic feature is the demonstration of storage iron. With iron deficiency stainable iron is never seen. Erythropoiesis is relatively retarded with infection whereas in iron deficiency erythropoiesis is active. In association with infection toxic granulopoiesis appears.

The differentiation of the anemia of infection from refractory anemia depends on the toxic changes in the bone marrow, the low serum iron, and the erythrocyte microcytosis, and hypochromia.

2. Refractory anemia of pregnancy. The criteria for establishing the diagnosis of refractory anemia of pregnancy include (1)

the appearance of anemia during pregnancy which disappears after delivery, (2) proved refractoriness to treatment, (3) a normal or elevated serum iron level, (4) thrombocytopenia and granulopenia, and (5) normoblastic hypoplasia. Variations from the above do occur. For many patients the diagnosis is one of exclusion. It is evident that no single determination or procedure is diagnostic of refractory anemia. The diagnosis depends to a considerable extent on the patient's refractoriness to adequately administered hematinics. To a lesser extent it is a laboratory diagnosis.

It would be most helpful if the diagnosis could be established with reasonable certainty on the basis of a bone marrow examination. In the majority of our patients with refractory anemia the bone marrow has been hypocellular with normoblastic hypoplasia. However, 2 of the patients were found to have hypercellular marrows with apparent active erythropoiesis. Although this paradox cannot be explained, Bomford and Rhoads¹⁷ established the reality of this finding for patients with refractory anemia not associated with pregnancy. In all the marrows properly stained for iron, storage iron was demonstrated.

The peripheral blood picture is not di-

agnostic, for the red cells are normocytic and normochromic. A normal or elevated serum iron excludes iron deficiency but does not exclude other types of anemia. Demonstration of a low reticulocyte count, thrombocytopenia, and leukopenia are helpful signs, for it is logical to assume that any factor influencing bone marrow function would depress all marrow elements; yet examples of pure erythroid hypoplasia without thrombocytopenia and leukopenia have been reported.¹⁸ Also, in megaloblastic anemia of pregnancy the platelets and leukocytes are characteristically diminished.

Comment

Considerable information about anemia of pregnancy has been amassed, but, understandably, most interest has centered around iron deficiency and megaloblastic anemia since they constitute the bulk of those commonly encountered. When the patients with hemoglobinopathies, iron deficiency, megaloblastic, and hemolytic anemias are sorted out from the total number with anemia of pregnancy, there remain a small number who exhibit refractoriness to therapy. In my experience this small group occurs in association with chronic infection or falls into the category of refractory anemia.

The diagnosis of anemia of infection is not a particular problem. The anemia assumes most of the characteristics of true iron deficiency except that a leukocytosis exists and the anemia is refractory to iron therapy.¹⁹ Not infrequently the demonstration of anemia refractory to iron has led to a rewarding search for a chronic urinary tract infection. If the infection is not clinically obvious the diagnosis depends on the demonstration of toxic granulopoiesis and iron deposits in the bone marrow.

The pathogenesis of anemia of infection is the same whether the patient is pregnant or not. Hemolysis is not a factor. In our patients no evidence for excessive blood destruction could be found. Anemia occurs, rather, because of retardation of hemoglobin synthesis.^{20, 21} As a consequence of the smaller hemoglobin mass and the re-

stricted iron demand, the extra iron is diverted to the storage areas. The clinical course of the anemia depends upon the recognition of the infection and its treatment, not on the administration of a hematinic. Once the infection has been removed, hemoglobin synthesis proceeds rapidly. For this purpose the stored iron is utilized. In most patients with anemia of infection the iron reserves are insufficient to completely meet the need; consequently, supplemental iron should be administered.

The varied hematologic picture of refractory anemia associated with pregnancy suggests that it is not a single entity but may represent several entities which cannot be recognized by existing laboratory procedures. Refractory anemia occurs with varying degrees of severity. The group of anemias which comprise this study were moderately severe. In each instance where information was available on other pregnancies a refractory anemia existed. Rovinsky¹¹ has documented 17 cases of severe refractory anemia, 1 of his own and 16 from the literature; 11 of the 17 terminated fatally. An interesting feature of all these cases is that the refractory anemia was precipitated by pregnancy, persisted for the duration of the pregnancy, but underwent spontaneous remission after delivery. This can only mean that some product of pregnancy alters bone marrow function.

There is no reason in the present state of our knowledge to separate the refractory anemias of pregnancy on the basis of their severity. It is more than probable that milder forms of refractory anemia exist but in this form they are difficult to recognize. In a series of patients with hemoglobin values ranging from 10 to 11 Gm. per cent intramuscular iron has proved to be ineffective on some of the patients. The addition of cobalt to the diet produced a response. Three patients in the series were demonstrated to have retarded erythrocyte production by means of radioiron utilization studies. It is my impression that these patients had refractory anemia, but other diagnostic signs were not present.

Recent investigations have disclosed a humoral factor which controls erythropoiesis.²² A satisfactory assay method has been developed, but, unfortunately, the method is not sensitive enough to detect normal or decreased concentrations of the so-called erythropoietic hormone. In our hands the assay has demonstrated serum activity following acute hemorrhage, in severe iron deficiency anemia, and in cobalt-stimulated animals. No activity has been found in normal pregnancy serum, cord blood serum, and, more specifically, from the serum of patients with refractory anemia.

The treatment of refractory anemia during pregnancy remains unsatisfactory. Cobalt may be tried, for this is the only element capable of bone marrow stimulation. The time required for a cobalt-induced response is great enough to minimize its effectiveness. One patient (M. R.) with proved refractory anemia successfully maintained normal hematologic levels in a second pregnancy on cobalt therapy. The usual therapy consists of whole blood transfusions at term to provide a satisfactory hemoglobin concentration at delivery for the patient's protection.

The diagnosis of refractory anemia of pregnancy requires a complete hematologic survey. The survey should be complete enough to exclude other types of anemia.

Refractory anemia is usually normocytic and normochromic. Other evidence of bone marrow depression may be found in low reticulocyte, platelet, and leukocyte counts. The serum iron is normal or elevated. A bone marrow examination, an essential part of the anemia investigation, most typically reveals normoblastic hypoplasia. Storage iron can be demonstrated.

Summary

1. The hematologic data and bone marrow morphology from 2 patients with anemia of infection and 13 patients with refractory anemia of pregnancy have been presented.

2. The diagnosis of anemia of infection is based on a low serum iron level, toxic granulopoiesis, and the demonstration of storage iron in the bone marrow.

3. The anemia of infection is refractory to treatment with iron. Remission follows appropriate antibiotic therapy.

4. The diagnosis of refractory anemia of pregnancy is based on the exclusion of other types of anemia, proved refractoriness to hematinics, a normal or elevated serum iron level, thrombocytopenia, and usually normoblastic hypoplasia of the bone marrow.

5. The bone marrow in association with refractory anemia may be hyperplastic. Storage iron can be demonstrated.

REFERENCES

- Holly, R. G.: *Obst. & Gynec.* 1: 535, 1953.
- Dobriner, K., Rhoads, C. P., and Hummell, L. E.: *J. Clin. Invest.* 17: 125, 1938.
- Hurwitt, E. S., and Field, L.: *AM. J. OBST. & GYNEC.* 43: 42, 1942.
- Bigby, M. A. M., and Jones, F. A.: *J. Obst. & Gynaec. Brit. Emp.* 53: 182, 1946.
- Dilworth, E. E., and Mays, C. R.: *AM. J. OBST. & GYNEC.* 54: 529, 1947.
- Dorgan, L. T., and McGaughey, H. S.: *AM. J. OBST. & GYNEC.* 61: 1390, 1951.
- Loring, T. W.: *Stanford M. Bull.* 11: 170, 1953.
- Lachmann, A., Lund, E., and Vinther-Paulsen, N.: *Acta obst. et gynec. scandinav.* 33: 395, 1954.
- Levine, B., and Rosenberg, D. V.: *Ann. Int. Med.* 41: 844, 1954.
- Dacie, J. V., Smith, M. D., White, J. C., and Mollin, D. L.: *Brit. J. Haematol.* 5: 56, 1959.
- Rovinsky, J. J.: *Obst. & Gynec. Surv.* 14: 149, 1959.
- Holly, R. G.: *Obst. & Gynec.* 2: 119, 1953.
- Holly, R. G.: *Bull. Univ. Minnesota Hosp.* 25: 134, 1953.
- Scott, J. M., and Govan, A. D. T.: *J. Clin. Path.* 5: 145, 1952.
- Beutler, E., Larsh, S. E., and Gurney, C. W.: *Ann. Int. Med.* 52: 378, 1960.
- Holly, R. G., and Grund, W. J.: *AM. J. OBST. & GYNEC.* 77: 731, 1959.
- Bomford, R. R., and Rhoads, C. P.: *Quart. J. Med.* 10: 175, 1941.
- Wintrobe, M. M.: *Clinical Hematology*, ed. 4, Philadelphia, 1956, Lea & Febiger.
- Kuhns, W. J., Gubler, C. J., Cartwright, G. E., and Wintrobe, M. M.: *J. Clin. Invest.* 29: 1505, 1950.

20. Cartwright, G. E., Lauritsen, M. A., Humphreys, S., Jones, P. J., Merrill, I. M., and Wintrobe, M. M.: *Science* 103: 72, 1946.
21. Bush, J. A., Ashenbrucker, H., Cartwright,

- G. E., and Wintrobe, M. M.: *J. Clin. Invest.* 35: 89, 1956.
22. Gordon, A. S.: *Am. J. Clin. Nutrition* 5: 461, 1957.

Discussion

DR. J. L. McKELVEY, Minneapolis, Minnesota. One of Dr. Holly's contributions has been the recognition and detailed study of what might be called Holly's disease, the pregnancy-specific anemia to which he originally gave the name "hypoplastic anemia of pregnancy" and which he now wishes to describe under the term "refractory anemia of pregnancy." This is characterized by high levels of iron in storage depots and as transport iron in serum, by the absence of response to hematinics with the probable exception of cobalt and usually by a hypoplasia of the erythroid line in the bone marrow. It is also characterized by a pregnancy specificity in that, so far as is known, once established, it recurs with each pregnancy and undergoes spontaneous remission at the end of each. Its basic feature seems to lie in the fact that something resembling a hypersensitivity response, peculiar to a few individuals and associated with pregnancy in them, interferes with the bone marrow production and release of erythrocytes. That it is now an established entity seems clear. The obvious significance of its recognition lies in the necessary avoidance in these iron-saturated individuals of the administration of massive quantities of iron and the avoidance of wasted time and money in the administration of forms of therapy which have been demonstrated to be without effect.

One wonders if the choice of a term to describe the entity is only an exercise in semantics. The term "refractory anemia" was originally used by the hematologists to describe a group of lesions which were not understood and which did not respond to usual therapy. Several of these have gradually yielded to investigation and one after another they have been taken out of the indefinite category and given specific and descriptive terms. It is important that the anemias of infection be recognized and the details which Dr. Holly has described be used for diagnosis and direction of therapy. That these details are quite different from those seen in this pregnancy-specific anemia is clear. To confuse them under a common term will only lead to a postponement of the

acceptance and recognition of the pregnancy-specific anemia.

Dr. Holly is bothered by the fact that 2 of his patients whose anemia apparently fitted otherwise into the category of the pregnancy-specific anemia showed the absence of an erythroid hypoplasia in the bone marrow. Would it not be the part of wisdom at the moment to accept the findings of hypoplasia in all of the others as characteristic of the disease and hope that further study would elucidate the exceptions? Is it possible that these 2 had an earlier iron deficiency with a later and recently superimposed hypoplastic or refractory anemia of pregnancy? What were the findings in one of these exceptions in a subsequent pregnancy?

Further studies of the effectiveness and eventually of the mechanisms of cobalt therapy are promising. It has apparently been possible in patients who were known to have had this specific anemia in previous pregnancies at least to hold blood hemoglobin levels during the present pregnancy by the administration of cobalt. Would Dr. Holly care to say something of his recent experiences with this?

Dr. Holly has used massive doses of intramuscular iron. This material has recently been withdrawn because of the production in the experimental animal of sarcomas which followed frequently repeated injections of the material. There are as yet no known reports of similar lesions in the human being. Does Dr. Holly know of any such?

DR. CURTIS J. LUND, Rochester, New York. The rarity of refractory anemia is well known and to have such a well-documented series of 11 patients is excellent. I mention 11 because I question why 2 patients with hypercellular marrow were included in the group. To be sure, these 2 cases are refractory but it seems to me that the series would have been so much cleaner had they not been included and had Dr. Holly clung to his former idea that this was hypoplastic anemia of pregnancy. This may be bordering on semantics.

The second point which might be made is a

purely practical one. How do you treat patients with severe degrees of hypoplastic anemia and what are your indications for blood transfusion therapy?

DR. ALBERT PLENTL, New York, New York. I would like to ask: Is the red cell survival time of any significance? Does it differ from that seen in any other anemia?

DR. HOLLY (Closing). With respect to the red cell survival, this factor was measured on some of the patients and was found to be normal. Urinary and fecal urobilinogen excretions were normal so there apparently was no undue breakdown of red cells.

As you perhaps gathered, there is a matter of semantics here which represents a change on my part. I am certain that by referring to this anemia as refractory anemia we are more closely following the accepted hematologic terminology. There are several other synonyms for these nonresponsive anemias: hypoplastic, aplastic, aregenerative, and myelophthisic, but the term preferred by most hematologists is refractory anemia. Since we have encountered 2 patients who did not have normoblastic hypoplasia I have felt it would be better to refer to the total group as having "refractory anemia of pregnancy." The terminology is confusing because we use the word "refractory" to refer to any anemia which does not respond to therapy. The term is also used by hematologists to refer to a specific anemia which is resistant to therapy and is not secondary to infection, chronic renal, hepatic, or malignant disease and

in which the disturbance probably is an alteration of bone marrow function.

Studies on the humoral factors which effect erythropoiesis have been carried out. I had hoped to have some significant material to present but to date all we have turned up are negative results. A satisfactory assay method has been developed. We have found that animals injected with cobalt and patients with severe iron deficiency anemia may have assayable quantities of erythropoietic hormone. Two of the patients with refractory anemia had no assayable erythropoietic hormone. We have not found it in normal pregnancy or in normal human serum. Until some method of concentrating human serum is found, the method can be useful only for detecting increased amounts of this specific hormone. Normal quantities and decreased quantities cannot be estimated by the method and for this reason it is not applicable at the present time to this study.

We have a series of patients with a less marked anemia than those presented here who have proved refractory to intramuscular iron and other forms of therapy. The addition of orally administered cobalt in each instance produced a satisfactory response. One patient in the series with refractory anemia in a later pregnancy received cobalt and maintained a normal hematologic level throughout her pregnancy.

As far as treatment is concerned, I believe cobalt is the only element that offers any possibility of producing a response. We give transfusions to those patients with hemoglobin levels of less than 10 Gm. per cent just prior to delivery.

Blood volume changes in pregnancy and the puerperium

I. Does sequestration of red blood cells accompany parturition?

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NUMEROUS investigators have measured the volume of circulating red blood cells prior to delivery and again early in the puerperium. Most have found that an appreciable quantity remains unaccounted for when the measured loss is compared to the much larger apparent decrease in the volume of circulating red cells. In these studies usually the circulating red cell volumes were estimated indirectly with Evans blue dye or radioiodine-labeled albumin. In a few instances the red cell itself was labeled with radioiron, radiophosphorus, or carbon monoxide to determine the volume of circulating erythrocytes.¹⁻⁷ The results of several of these investigations are summarized in Table I.

No satisfactory explanation has been offered to account for the marked lack of agreement between the smaller volumes of

red cells demonstrated to have been lost by direct measurement and the much larger loss by difference. Even more difficult to explain is the observation that often at the time of vaginal delivery, but not delivery by cesarean section, there appears to be a rather marked and about equal increase in both the plasma volume and the red cell volume above the predelivery level. This increase is followed soon after delivery by a much larger decrease.⁸

These reported changes have been interpreted to indicate that during parturition and early in the puerperium red blood cells are not free in a single intravascular compartment. Instead, there must be at times compartmentalization of maternal blood with marked retardation of movement of erythrocytes between these compartments. The alternative is that the methods used previously to measure red cell volumes before, during, and after parturition have frequently yielded rather consistent but erroneous results.

It was decided to repeat these previous studies and to measure the volume of circulating red cells before and after delivery to compare the loss by difference with the loss determined by direct measurement. If the previously reported discrepancies between apparent and directly measured losses of red cells were confirmed, the site or sites

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of sequestration would be searched for and the fate of the sequestered red cells investigated.

Methods and materials

A most satisfactory material for labeling red cells is radioactive chromium in the form of sodium chromate. The subject's own red cells rapidly bind most of the isotope in vitro, and the unbound chromium can be easily removed by washing the red cells with saline. Once bound by the red cell, the radiochromium is eluted at a very slow rate.⁹ Moreover, previous studies have shown that when red cells labeled in this way were injected intravenously into pregnant women no detectable radioactivity subsequently appeared in the fetus.¹⁰

One hundred to 150 μc of $\text{Na}_2\text{Cr}^{51}\text{O}_4$ and 20 to 30 ml. of the subject's blood were placed in a 100 ml. silicone-coated bottle containing special formula acid-citrate-dextrose solution.* Forty to 50 μc of $\text{Na}_2\text{Cr}^{51}\text{O}_4$ can be used so that the total dose per determination is only 10 to 12 μc , or less than one thirtieth of the maximum dose allowed by the Atomic Energy Commission. One hundred to 150 μc was used during this study to facilitate the measurement of the volume of red cells collected at the time of delivery or operation. This mixture was then incubated for about 10 minutes at 37° C. or for approximately 20 minutes at room temperature. About 80 per cent of the chromium was bound by the red cells at the completion of the incubation. To the bottle was then added about 80 ml. of saline to nearly fill it. After agitation, the mixture was centrifuged in a Model SBC international centrifuge at 2,500 r.p.m. for about 15 minutes. The supernatant was aspirated and the washing process was repeated. After the second washing 1 per cent or less of the total chromium was unbound. Eighty to 90 ml. of saline was again added to the flask and the contents thoroughly agitated until the red cells were distributed uniformly.

*Commercially distributed by Abbott Laboratories, Inc., North Chicago, Illinois.

An ordinary 20 ml. sterile syringe was loaded exactly to the 20 ml. mark and the suspension of labeled red cells was injected intravenously. About 8 ml. of blood was drawn from the opposite arm 20 to 30 minutes after injection of the labeled cells. A minimum of 20 minutes was chosen since it had been noted that in some pregnant patients mixing of the red cells did not appear to be complete in less than 15 minutes. The blood was collected in dried balanced oxalate and its hematocrit was determined in duplicate. Four milliliters was measured precisely into a stoppered glass tube and then the red cells were lysed by freezing and thawing before counting in a well-type scintillation counter.

After cleaning and autoclaving, the same syringe filled in exactly the same way was used for the next injection of labeled red cells. Just prior to and again 20 to 30 minutes after the injection of the labeled cells, specimens of blood were again obtained for measurements of radioactivity and hematocrit.

The syringe was once again filled in precisely the same way with the suspension of labeled red cells and then emptied into a 2,000 ml. volumetric flask. This was filled with tap water and the contents thoroughly

Table I. Summary of previous investigations of the apparent decrease in whole blood and red blood cell volumes resulting from delivery

Investigator	Technique	Number of subjects	Observed decrease		Measured blood loss (ml.)
			RBC (ml.)	Blood volume (ml.)	
McLennan and Thouin ¹	Evans blue	20	321	852	---
Lowenstein et al. ²	Evans blue	9	392	1,041	306
Caton et al. ³	Fe ⁵⁵	5	523	1,635	---
Verel et al. ⁴	P ³²	5	581	1,620	920
Robbe and Ström ⁵	CO	18	355	961	547
Venning et al. ⁶	I ¹³¹	5	544	1,510	---
Statzer ⁷	I ¹³¹	7	159	461	---

mixed. Four milliliter aliquots of this standard mixture were measured out for determinations of radioactivity.

The apparent volume of distribution of the injected red cells was calculated as follows: Apparent blood volume times activity per milliliter of blood equals 2,000 times activity per milliliter of standard, or apparent blood volume = $\frac{2,000 \times \text{activity of standard}}{\text{activity of blood}}$.

The total red blood cell volume was determined from the apparent blood volume and the venous hematocrit: Total red cell volume equals apparent blood volume times venous hematocrit. This method measures circulating red cell volume. The volume of whole blood and plasma are calculated rather than measured values. No correction has been made for any difference between the venous and total body hematocrit determinations.

Correction for red cell radioactivity remaining from previous injections was necessary during subsequent measurements of the total volume of circulating red cells. If the hematocrit values of the preinjection and postinjection blood specimens were identical, the radioactivity resulting from subsequent injection was determined simply by subtracting the former from the latter. Not infrequently, however, the measurements of hematocrit were not exactly the same. In fact they were observed to change quite rapidly after delivery. In such circumstances, since the radioactivity occurred only in the red cells and was not distributed evenly between cells and plasma, the radioactivity of the former had to be corrected to the activity it would possess if its hematocrit were the same as that of the postinjection specimen. This, in effect, was equivalent to always measuring out and counting the radioactivity of an identical volume of red cells, but was technically much more simple and probably more accurate.

If a third determination of circulating red cell volume was desired, the steps outlined for the second determination were repeated. The labeled red cell suspension kept refrigerated was used for 18 to 24 hours after its preparation with apparently little immediate

loss of red cell integrity and with no harm to the recipient.

A number of studies were carried out to check the validity of this method for measuring the total volume of circulating red cells. By means of the above technique it was measured twice in each of 6 undelivered pregnant women who were at or near term. Some were in active labor during at least the second determination. The circulating red cell volume was next measured before and immediately after removal of a known volume of blood by venesection from 4 non-pregnant women and from 2 near-term pregnant women. In one of the latter the total red cell volume was measured again after returning the blood withdrawn from her.

To determine what effects, if any, anesthesia and the lithotomy position might have, the total red cell volume was measured in 2 women before and after diagnostic uterine curettage and in 2 women before and after vaginal hysterectomy plus anterior and posterior colporrhaphy. Blood lost during these procedures was collected and treated as described below.

Total red cell volumes were measured before and after delivery and the total red cells lost during this period were collected quantitatively in 24 instances. In 16 of these vaginal delivery was performed, in 2 cesarean section was carried out, and in 6 cesarean hysterectomy was performed. All blood lost up until the time of the injection of labeled red cells after delivery was collected. In the case of vaginal deliveries most of the blood lost was collected with use of pans and rubberized sheets under the perineum. When delivery was carried out transabdominally, 2 suction aspirators were used and nearly all of the blood lost was collected through them. All sponges and grossly soiled linen and the placenta were collected, as was the uterus, when a hysterectomy was performed.

The aspirated liquid blood and any clots were thoroughly mixed in a Waring Blendor. The placentas and uteri were ground with a commercial meat grinder and then homogenized in a Waring Blendor with added

water. After drying, the linen and sponges were washed and wrung out twice in a washing machine containing a known quantity of water. This produced complete extraction of the radiochromium from the linen and sponges. Several 4 ml. aliquots of each were taken and the radioactivity of the aliquots was determined. In this way homogeneity was assured. The total radioactivity obtained divided by the activity per milliliter of circulating red cells yielded the volume of red blood cells contained. In a few instances the hemoglobin content of the aspirated blood and blood clots was measured directly as cyanmethemoglobin. The total hemoglobin content determined spectrophotometrically equaled the amount calculated to be present from the total radioactivity divided by the radioactivity per gram of circulating hemoglobin.

Fifteen of the placentas and their membranes, including those from one set of twins, were wiped free of surface clots and processed as described above to determine the volume of maternal red cells trapped within them.

Results

All studies performed showed good agreement between red cell losses when determined by difference and by direct measurement. Duplicate measurements of the total circulating red blood cell volume in term or near-term subjects in the absence of any blood loss yielded nearly identical results. The difference between the means of the total circulating red cell volumes was 12 ml., or 0.5 per cent. The individual determinations are listed in Table II.

As shown in Table III, in 4 nonpregnant and 2 near-term pregnant women there was excellent agreement between the volume of red cells removed by venesection when determined by difference and when measured directly. The decrease in total circulating red cell volume by difference was 165 ml. and by direct measurement 172 ml.

When the effect of anesthesia plus lithotomy position was investigated, with and without appreciable blood loss but in the

Table II. Repeated measurements of red blood cell volumes in near-term or term pregnant women prior to delivery

	<i>Cr⁵¹</i> RBC volume (ml.)		<i>Difference</i> (%)	<i>Interval</i> (hr.)
	<i>First</i>	<i>Second</i>		
1	2,205	2,145	-2.7	23
2	1,790*	1,780*	-0.1	3
3	1,275	1,240*	-2.7	144
4	1,805	1,680*	-7.0	21
5	1,695	1,780*	+5.1	20
6	1,880	1,955	+4.0	3
Average	1,775	1,763	-0.5	

*Active labor.

Table III. Comparison of red blood cell loss determined by difference and by direct measurement in nonpregnant and in near-term pregnant women subjected to venesection

		<i>Cr⁵¹</i> red cell volume (ml.)		<i>Difference</i>	<i>Directly measured</i> (ml.)
		<i>Initial</i>	<i>Final</i>		
1	Nonpregnant	1,460	1,290	170	190
2	Nonpregnant	1,235	1,020	215	196
3	Nonpregnant	1,440	1,275	165	179
4	Nonpregnant	1,380	1,180	200	204
5	Pregnant	1,340	1,215	125	141
6	Pregnant	1,040*	925	115	122
Average		1,316	1,151	165	172

**Cr⁵¹* red cell volume after return of withdrawn blood 1,050 ml. compared to 1,040 ml. found originally.

Table IV. Comparison of red blood cell loss determined by difference and by direct measurement in subjects undergoing anesthesia and vaginal operation

	<i>Cr⁵¹</i> red cell volume (ml.)			<i>Directly measured</i> (ml.)
	<i>Initial</i>	<i>Final</i>	<i>Difference</i>	
Diagnostic curettage	695	690	-5	< 5
Diagnostic curettage	1,320	1,330	+10	< 5
Vaginal hysterectomy and colporrhaphy	1,450	1,190	-260	247
Vaginal hysterectomy and colporrhaphy	1,305	875	-430	405

absence of pregnancy, it was apparent that under these circumstances significance could be attached to any fluctuations found in the total volume of circulating red blood cells. When only a diagnostic uterine curettage was performed there was no difference between the preoperative and postoperative volumes of circulating red blood cells. When vaginal hysterectomy and colporrhaphy were carried out there was an appreciable drop in the volume of circulating red blood cells, but the decrease was almost identical to the volume of red blood cells demonstrated by direct measurement to have been lost. These data are presented in Table IV.

Red cell loss associated with parturition when measured directly and by difference

with use of this method failed to reveal the marked disparity previously found by others. The individual measurements in 16 vaginal deliveries, 2 cesarean sections, and 6 cesarean hysterectomies are shown in Table V. The mean red cell loss by difference in the vaginal delivery group was 219 ml. while by direct measurement it was 214 ml. In the case of cesarean section it was 185 ml. by difference and 163 ml. directly, and with cesarean hysterectomy it was 462 ml. by difference and 450 ml. by direct measurement.

A placenta wiped free of gross clots was found to contain on the average 30 ml. of maternal red cells, equivalent to 79 ml. of blood. Twice this amount was found in the

Table V. Comparisons of volumes of red blood cells lost during parturition when measured directly and by difference

	Apparent blood volume		Hematocrit		RBC volume			Direct measure
	Initial	Final	Initial	Final	Initial	Final	Difference	
A. Vaginal delivery								
1	5,380	4,455	39.0	44.0	2,100	1,960	140	90
2	4,630	4,060	37.5	39.0	1,735	1,580	155	150
3	3,415	2,640	41.0	44.0	1,400	1,160	240	255
4	4,125	3,840	40.0	39.5	1,650	1,515	135	190
5	3,950	2,960	34.0	37.0	1,345	1,090	255	290
6	3,720	3,105	39.0	39.0	1,450	1,210	240	295
7	3,175	2,740	29.0	29.0	920	795	125	180
8	3,910	3,140	36.0	40.0	1,405	1,255	150	105
9	3,630	3,295	31.0	30.5	1,125	1,005	120	90
10	4,090	3,400	43.5	40.0	1,780	1,360	420	370
11	3,910	3,040	33.5	36.5	1,310	1,110	200	130
12	3,620	3,470	33.5	32.0	1,210	1,110	100	125
13	4,520	3,790	44.0	44.0	1,990	1,665	335	265
14	4,480	3,860	40.0	45.0	1,790	1,690	100	135
15	4,750	3,450	42.0	40.0	1,995	1,380	615	590
16	3,350	3,000	42.0	41.0	1,410	1,230	180	165
Average	4,050	3,390	37.8	38.8	1,538	1,319	219	214
B. Cesarean section								
1	4,135	2,920	35.0	42.5	1,445	1,240	205	200
2	4,500	3,760	40.5	44.0	1,820	1,655	165	125
Average	4,320	3,340	37.8	43.3	1,633	1,448	185	163
C. Cesarean hysterectomy								
1	4,250	3,305	41.5	43.0	1,765	1,420	345	390
2	4,250	2,820	37.0	39.5	1,570	1,110	460	460
3	5,850	4,910	38.0	34.5	2,220	1,690	530	620
4	4,680	3,690	34.0	34.0	1,590	1,220	370	300
5	4,280	2,770	38.5	39.0	1,645	1,080	565	495
6	4,595	2,860	34.0	37.0	1,560	1,060	500	435
Average	4,650	3,395	37.2	37.8	1,725	1,263	462	450

Table VI. Maternal red cells contained in the placenta after delivery

	RBC (ml.)	Blood (ml.)	Predelivery hematocrit
1	32	91	33.5
2	24	63	38.5
3	20	55	34.0
4	26	83	31.0
5	40	102	35.0
6	38	100	38.0
7	35	101	34.0
8	22	55	37.0
9	26	62	42.0
10	40	110	36.0
11	45	104	41.0
12	21	62	33.0
13	21	50	40.5
14*	61	166	36.5
15*			
Average	30	79	37.0

*Placentas from twins.

combined placentas from twins. These data are presented in Table VI.

In 20 instances the radioactivity per unit of red cells at the time the first blood sample was collected was compared to the radioactivity present in an equivalent volume of red cells collected after vaginal delivery prior to the second injection of labeled red cells. The interval between collections ranged from 2½ to 40 hours and averaged 14 hours. In all cases the initial specimen was collected more than 1 hour before delivery and the second was collected more than 1 hour after delivery of the placenta. As shown in Table VII, radioactivity per unit of red cells decreased on the average only 1.4 per cent during the 14 hours between the first and second collection.

Comment

Consistently throughout this study the magnitude of the decrease in the volume of circulating red blood cells was in close agreement with the amount determined to have been lost by direct measurement. Therefore, these data do not agree with those of several previous investigations.

As a consequence of delivery, how could an appreciable decrease in the volume of circulating red blood cells considerably in

excess of the amount lost by direct measurement be effected? The possibilities seem to be (1) intense erythrocyte destruction, (2) sequestration of an appreciable volume of red blood cells somewhere in the body, (3) a combination of these two processes. Hemolysis of sufficient intensity to account for the apparent loss of red blood cells reported previously would be accompanied by icterus and other stigmas of red cell destruction. Gross hemolysis, therefore, can be excluded. If sequestration is the answer, where are these red blood cells sequestered? The uterus has been suggested.² If this were true, it follows that a difference would have been noted during this study in the pattern of response in the group subjected to hysterectomy at the time of delivery and the group delivered without hysterectomy. No difference was found.

Table VII. Comparison of the circulating red blood cell radioactivity 20 to 40 minutes after predelivery injection of labeled red cells and of the same volume of red blood cells withdrawn after vaginal delivery

	Radioactivity per unit of red cells		Interval between first and second blood sample (hours)
	Initial	Final	
1	6,820	6,710	5½
2	6,330	6,285	5
3	7,900	8,110	18
4	12,770	12,670	1
5	5,765	5,380	40
6	9,100	9,610	6
7	5,260	5,120	22
8	6,450	6,560	16
9	6,240	5,970	23
10	4,355	4,230	20
11	13,745	14,400	2½
12	6,640	6,470	3
13	10,995	10,610	18
14	7,435	6,980	22
15	6,040	5,995	22
16	18,790	18,200	19
17	7,390	7,180	4
18	8,510	8,340	6
19	8,580	8,170	20
20	10,960	10,690	4½
Average	8,500*	8,385*	14

*Therefore, 1.4 per cent decrease in radioactivity per unit of red cells during an average interval of 14 hours.

Tatum⁸ has described an abrupt increase in blood volume about the time of vaginal delivery. Since the hematocrit determination did not change significantly at this time, these observations were interpreted to indicate that a considerable volume of both red cells and plasma mobilized from unknown sites appeared rather suddenly in the intravascular compartment. This blood, plus considerably more, then quite rapidly disappeared so that a few hours after delivery the blood volume and the volume of circulating red cells were presumably considerably less than prior to delivery.

Chromium-labeled erythrocytes remain labeled throughout their life span. There is no transfer of chromium from one red blood cell to another. If red blood cells are added to the circulation by transfusion, the radioactivity per unit of circulating red blood cells falls proportionate to the volume of cells added to the intravascular compartment. If the observations of Tatum did not result from artifact, the movement of erythrocytes from some undetermined site of sequestration into the intravascular compartment should by dilution have caused a concomitant fall in the radioactivity per unit of circulating red blood cells about the time of delivery and thereafter. Such a dilution by unlabeled erythrocytes was never found.

Finally, the technique described under "Methods and materials" for measuring red cell loss and indirectly whole blood loss by difference has been applied to date in 65 vaginal deliveries and 35 repeat cesarean sections. As the result of vaginal delivery, red cells equivalent on the average to 455 ml. of whole blood disappeared from the circulation. Newton and co-workers¹¹ at the 1960 meeting of the American College of

Obstetricians and Gynecologists reported that by the end of the first hour after delivery whole blood loss by direct measurement in 100 vaginal deliveries averaged 380 ml. If the volume of maternal blood trapped in the placenta is added to 380 ml., the total loss found by each method is practically the same. Moreover, as a result of cesarean section, red cells equivalent to 980 ml. of whole blood disappeared from the circulation. Wilcox, Hunt, and Owen¹² have recently reported that blood loss at the time of cesarean section determined by direct measurement in 25 instances averaged 1,028 ml. Again, the losses by difference and by direct measurement are almost identical.

It is gratifying to find that the application of this technique of measuring red cell loss by difference to a rather large number of cases yields results comparable to those obtained by other investigators who quantitated blood loss by direct measurement. These observations, however, fail to account for the discrepancy between the results of this study of the volume of maternal red cells circulating before and after delivery and the reports of previous investigators.

Summary and conclusions

The volume of circulating red blood cells was measured before and after delivery and the decrease compared to the volume determined to have been lost by direct measurement.

The previously reported apparent sequestration of large volumes of red blood cells as the result of delivery was not confirmed. No evidence was found which would indicate that sequestration of maternal red blood cells accompanies parturition.

REFERENCES

1. McLennan, C. E., and Thouin, L. G.: *AM. J. OBST. & GYNEC.* 55: 189, 1948.
2. Lowenstein, L., Pick, C. A., and Philpott, N. W.: *AM. J. OBST. & GYNEC.* 60: 1206, 1950.
3. Claton, W. L., Roby, C. C., Reid, D. E., Caswell, R., Maletskos, C. J., Fluharty, R. G., and Gibson, J. G., II: *AM. J. OBST. & GYNEC.* 61: 1207, 1951.
4. Verel, D., Bury, J. D., and Hope, A.: *Clin. Sc.* 15: 1, 1956.
5. Robbe, H., and Ström, G.: *Acta obst. et gynec. scandinav.* 37: 448, 1958.
6. Venning, E. H., Dyrenfurth, I., Lowenstein,

- L., and Beck, J.: *J. Clin. Endocrinol.* 19: 403, 1959.
7. Statzer, D. E.: *Obst. & Gynec.* 14: 37, 1959.
8. Tatum, H. J.: *AM. J. OBST. & GYNEC.* 66: 27, 1953.
9. Ebaugh, F. G., Emerson, C. P., and Ross, J. F.: *J. Clin. Invest.* 32: 1260, 1953.
10. Pritchard, J. A.: Unpublished observations.

11. Newton, M., et al.: Data presented before the American College of Obstetricians and Gynecologists, Cincinnati, Ohio, April 6, 1960.
12. Wilcox, C. F., III, Hunt, A. B., and Owen, C. A., Jr.: *AM. J. OBST. & GYNEC.* 77: 772, 1959.

Discussion

DR. CHARLES E. McLENNAN, Palo Alto, California. Discussion of an experiment of this type could involve hours of debate about methodology, magnitude of experimental error, correction factors, and other technical details of concern only to those intimately associated with studies of the vascular system and its content. Assuming, and I hope correctly, that not many present today are deeply concerned about such matters, I shall confine my attack to just a few of the more general statements in this nicely executed paper.

To begin with, in the opening paragraph I find myself and my associate blanketed with 6 other investigators (or groups of workers) who seem to have suggested the occurrence of a mysterious and unaccountable loss of red blood cells during labor or early in the puerperium. I wish to remove myself at once from this little fraternity of clinicophysiology and to point out that no such suggestion has been made in any of my publications concerning blood volumes in pregnancy.

Actually, I find on reviewing a paper I read before this Society in 1947 that Dr. Pritchard and I are in close agreement on at least one point. His group of 16 women who were delivered vaginally lost on the average 14.2 per cent of their original red cell volume in less than 2 days after delivery, whereas our 20 patients lost 16 per cent in 7 days. This does not appear to be a major discrepancy, particularly when one considers that some loss of hemoglobin continues well beyond the second puerperal day. Data from Robbe and Ström's recent study (their Table III) indicate that about 10 per cent of the hemoglobin lost in the first postpartum week disappears on Days 3 to 7, inclusive. It must be carefully noted, however, that our patients in Salt Lake City (and others in San Francisco) had much more blood to spare than did Dr. Pritchard's, and indeed it appears that their absolute losses were appreciably greater, although relatively they were of the same magnitude.

This raises the question of why blood volumes in Texas are so disconcertingly low. Dr. Pritchard encountered a group of women whose mean total blood volume was a mere 4 L. at term. To the statistician's view, then, he was working with a different sample of the population from that available to all other investigators, each of whom invariably has found the mean value for total blood volume to fall between 5.1 and 5.7 L. Does this reflect a peculiarity of the radiochromium method, or do Dallas women really have less blood? On this score they are tremendously different from Duncan Reid's Bostonian women with 5.74 L. at term. No simple explanation for this discrepancy is apparent to me at the moment, but I hope Dr. Pritchard can supply one.

If we look closely at the data and conclusions of some of the previous reports that have stimulated Dr. Pritchard, we find that the situation may not be so mysterious as he has hinted. Caton and Reid, for instance, found an average decline in red cell volume of approximately 200 ml. (as did the Dallas group), but since their figures showed about 1.2 L. loss of total blood volume they concluded that "this decrease is almost entirely due to plasma volume as the red cell volume has not decreased appreciably." No mention was made of sequestered cells. On the other hand, I must admit that Verel and co-workers said: "Twelve hours postpartum a marked fall in red cell volume has been demonstrated which is not explained by the blood lost at and after delivery." This seems to be making the most out of meager data (an old British custom), since examination of the published figures shows that only 1 out of 13 patients was studied 12 hours post partum with respect to both calculated and measured blood losses; the calculated red cell loss in this single instance was 230 ml., the measured red cell loss was 130 ml., and the clinician's estimated loss was 230 ml. (presumably whole blood). Statzer's group of 7 patients also showed an immediate postpartum loss of approximately 200 ml. in red cell volume,

and he pointed out again that the major loss of volume was from the plasma component.

Lowenstein and Philpott were concerned about apparent decreases in red cell volume occurring 36 to 48 hours after delivery and made the rather untenable suggestion that red cells were hiding out in the uterus. Inasmuch as their calculations were based on plasma volume measurements with Evans blue, I suspect that their indirectly computed red cell values were invalidated by rapid changes of intravascular volume which seem to occur in the first few postpartum days. This phenomenon has been mentioned in a number of papers and I have recently confirmed it, at least to my own satisfaction (Stanford Med. Bull. 17: 152, 1959).

Our study of 61 women at term and at various times during the first 3 days after delivery showed a drop in blood volume during the first 24 hours after delivery, but between 24 and 48 hours post partum there was a rise on the average of about 400 ml., a statistically significant amount. By the end of the third day the trend in blood volume was generally downward again. Finally, Robbe and Ström were unable to account for about a third of the calculated puerperal red cell loss, but admitted to many sources of error in their carbon monoxide method for estimating total hemoglobin and said they ignored placental blood because they didn't know how much placentas contained. This study, despite its careful planning and detailed execution, has merely added to the existing confusion.

In the main, then, I believe the published data are not convincingly at variance with what Dr. Pritchard has told us, and I suspect he may be perfectly right in claiming that red cells which disappear from the circulatory system at the time of delivery can be accounted for quite accurately if one goes about it properly. Indeed, many of his calculated and measured losses are so nearly identical as to arouse in the reader either admiration or skepticism. In one instance,

for example, red cell volume was measured in a nonpregnant subject before and after removal of 204 ml. of cells by venesection; the calculated loss turned out to be 200 ml. This degree of technical precision tempts me to start all over again to explore the ups and downs of blood volume in pregnancy and the puerperium, because I feel that the whole story has not been thoroughly documented. If this were to be undertaken, certainly one should use a technique for red cell volume that is not dependent on the venous hematocrit value, and simultaneously plasma volume should be assessed by means of a different labeling device.

DR. LOUIS M. HELLMAN, Brooklyn, New York. The figure of 79 ml. of maternal blood remaining in the placenta is one which I do not believe we have previously had available. I expect Dr. Pritchard thinks that during delivery some of the maternal blood is lost from the placenta, since the estimated volume before delivery is 100 ml., and this figure of 79 ml. remaining is in good agreement.

I would like to ask if any chromium-labeled red cells were lost to the baby?

DR. PRITCHARD (Closing). Throughout this presentation I had hoped to emphasize that the measurement actually being made was the volume of circulating red blood cells. Whole blood volume can be *calculated* from the volume of red blood cells and the venous hematocrit. There will be an error in so doing, the degree of which will depend upon the difference between the measured hematocrit of blood from a large vein and the undetermined mean total body hematocrit.

With the described technique for measuring red blood cell volume, the mean value for apparently normal nonpregnant women was 25 ml. per kilogram. This is almost identical to the values found by Huff with Cr⁵¹ and Berlin with P³² to label erythrocytes.

Plasma nonesterified fatty acids in pregnancy

II. Experimental modification

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IN A previous report the marked increase in nonesterified fatty acid (NEFA) concentration of plasma in late pregnancy was described.⁵ The factors responsible for this, as well as the basis for the increased concentration of other plasma lipids, remain unknown, but because of the reported similarity to plasma lipid patterns in diabetes this lipemia may represent another aspect of the diabetogenic effect of pregnancy. The present study is an extension of our original observations concerning plasma NEFA, and it further characterizes the metabolic status of normal and toxic pregnancy.

Our primary interest in NEFA derived from the suggested relationship of this lipid fraction to carbohydrate metabolism. In normal subjects the concentration of NEFA in peripheral plasma and its rate of release from lipid depots appears to depend upon the availability of glucose and ability of the patient to utilize carbohydrate. In starvation, when carbohydrate sources are poor, increments in the NEFA fraction occur,^{11, 13} and in the patient with uncontrolled diabetes increases are regularly observed.¹ In fasting subjects the administration of insulin, tol-

butamide, glucose, or fructose is followed by decreases in plasma NEFA,^{2, 11, 12} although the change after insulin treatment is markedly affected by the administration of glucose.⁹ The NEFA fraction which appears to be the major component of the total lipid transport mechanism from storage depots to the tissues turns over very rapidly^{3, 4, 15} and, because of the close reciprocal relationship between fatty acid release and the level of carbohydrate utilization, NEFA may provide for "caloric homeostasis,"⁴ rapidly supplying energy when carbohydrate either is not available or, by reason of metabolic error, cannot be utilized. The observations to be reported may be of interest not only as they relate to carbohydrate metabolism in the diabetogenic circumstance of pregnancy but because of their possible bearing on the factors regulating NEFA circulation in peripheral plasma.

Materials and methods

Groups of 20 normal subjects between 36 weeks of gestation and term were studied under basal conditions after they fasted 15 to 18 hours. One group received intravenously 0.1 unit of regular HGF-free insulin* per kilogram of body weight. A second group received 20 mg. tolbutamide† per kilogram by vein. A limited number of pre-eclamptic patients were likewise studied with

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*Regular insulin free of hyperglycemic-glycogenolytic factor was supplied through the courtesy of Dr. W. R. Kirtley, Eli Lilly & Company, Indianapolis, Indiana.

†Orinase furnished through the courtesy of Dr. C. J. O'Donovan, The Upjohn Company, Kalamazoo, Michigan.

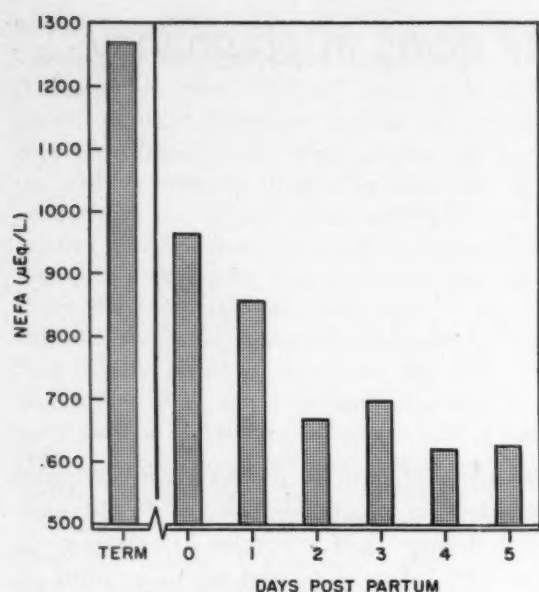


Fig. 1. Mean values for plasma NEFA from term through the fifth postpartum day.

either insulin or tolbutamide. Normal nonpregnant subjects were tested for comparative control data.

Additional individual plasma NEFA determinations were made on nonpregnant subjects and on normal patients at term and during the early puerperium after uncomplicated vaginal delivery as follows: 36 at term; 303 observations between the day of delivery and the fifth postpartum day; 79 individual determinations on nonpregnant control subjects.

After a pretest blood sample, venous blood was obtained without stasis at 30 minute intervals up to 3 hours after insulin or tolbutamide treatment. The total nonesterified fatty acids in plasma aliquots were determined by the method of Dole. Blood glucose was estimated by the Somogyi-Nelson technique and plasma inorganic phosphate by the method of Fiske and SubbaRow as previously described.⁶

Observations

In Fig. 1 are graphically shown the plasma levels of NEFA observed between term and the fifth postpartum day. The mean value found for 36 subjects at 40 weeks' gestation was $1,267 \pm 343$ μEq per

liter compared to 724 ± 184 for 79 normal nonpregnant control subjects. In the pregnant series occasional values in excess of 1,800 μEq per liter were observed. The prompt return toward normal or low normal NEFA levels in the early puerperium is also shown in Fig. 1. The value of 627 ± 170 μEq per liter for 62 subjects was observed on the fifth postpartum day. These values are given in Table I.

The results of administration of 0.1 insulin per kilogram of body weight to subjects between 36 and 40 weeks of gestation are plotted in Fig. 2. The initial depression in NEFA reaches a minimum value in 30 minutes, following which successive values increase for the duration of the experimental period. The "rebound" above fasting pretest values is in excess of 400 μEq per liter. In separate experiments without insulin treatment and under comparable conditions of fasting no significant increase in NEFA was observed during the 3 hour period of observation. The characteristic hypoglycemia and hypophosphatemia developing after insulin is also shown in Fig. 2. Control data are plotted in Fig. 3. Attention is directed to the abrupt and sharp fall in blood sugar level as well as the somewhat more marked fall

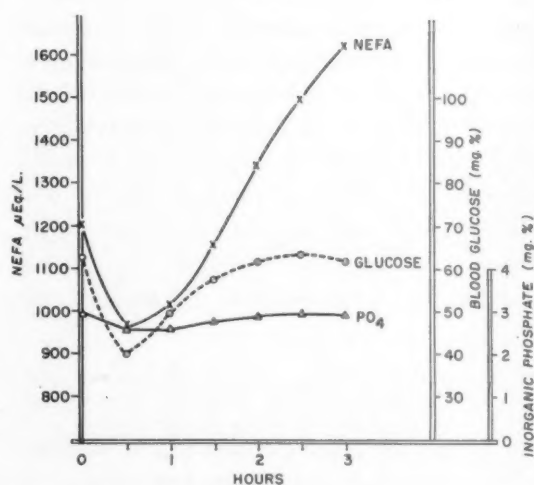


Fig. 2. Changes in NEFA, glucose, and plasma, inorganic phosphate following administration of 0.1 unit HGF-free insulin per kilogram body weight intravenously. Mean values are shown for 20 subjects.

in phosphate compared to that observed for pregnant subjects (Fig. 2). Despite the obvious and significant differences in reactivity to insulin in terms of hypoglycemia ($P = < 0.001$) and hypophosphatemia, the absolute changes in NEFA concentration are comparable for pregnant and control groups. This is shown in Fig. 4, where mean decrements or increments from fasting levels for glucose and NEFA are plotted. At one-half hour a slight tendency to divergence of the mean NEFA values appears, but at the vari-

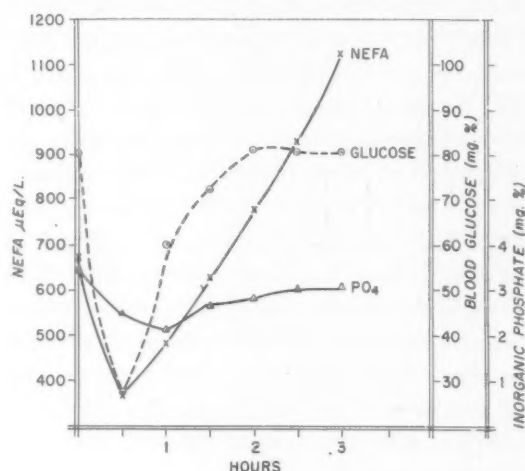


Fig. 3. Changes in NEFA, glucose, and inorganic phosphorus for control subjects receiving 0.1 unit HGF insulin per kilogram body weight. Mean values are shown for 20 subjects.

ance observed this difference is not statistically significant ($P = 0.9$). The development of insulin resistance as evidenced by hypoglycemia is not attended by a corresponding change in NEFA response, which is quantitatively identical for pregnant and control groups.

The characteristic changes in blood glucose, plasma inorganic phosphate, and NEFA after tolbutamide administration are shown in Fig. 5 for pregnant subjects. During the experimental period of observation the NEFA changes were quite different from those observed for insulin. Not only was the decrement greater ($-489 \pm 249 \mu\text{Eq}$ per liter at one hour compared to the maximum decrease of -222 ± 120 for insulin at one-half

Table I. Mean values for nonesterified fatty acids of plasma from term through the fifth postpartum day

	No.	NEFA ($\mu\text{Eq/L.}$)
Nonpregnant	79	724 ± 184
Term	36	1267 ± 343
Day of delivery	28	961 ± 339
First postpartum day	60	859 ± 276
Second postpartum day	46	669 ± 223
Third postpartum day	46	698 ± 231
Fourth postpartum day	61	621 ± 199
Fifth postpartum day	62	627 ± 170

hour) but during the experimental period rebound above fasting was not observed.

In postpartum and nonpregnant subjects receiving tolbutamide the changes in NEFA showed no significant differences from those observed for subjects between 36 and 40 weeks despite greater inorganic phosphate and glucose falls. (Δ glucose at one-half hour 35.7 ± 14 mg. per cent, nonpregnant; 10.2 ± 10 mg. per cent, pregnant). Mean values for NEFA are shown for these subjects in Fig. 6.

The mean values for NEFA obtained on 10 pre-eclamptic patients after treatment with tolbutamide were not significantly different from those for normal pregnancy or the control group. In 5 additional pre-eclamptic patients tested with insulin, the pattern of the NEFA response was likewise indistinguishable from that of normal pregnant or control subjects despite markedly attenuated glucose and phosphate falls.

Comment

It is apparent from the data presented that the NEFA fraction participates in the hyperlipidemia of pregnancy. Significant increases are seen particularly from 36 weeks to term with rather prompt return to normal levels 36 to 48 hours after delivery in uncomplicated puerperal patients. Whether the observed increases in the nonesterified fatty acids are based on gestational changes in rates of release from lipid depots or decreased utilization of circulating lipid is uncertain. It is possible that both release and

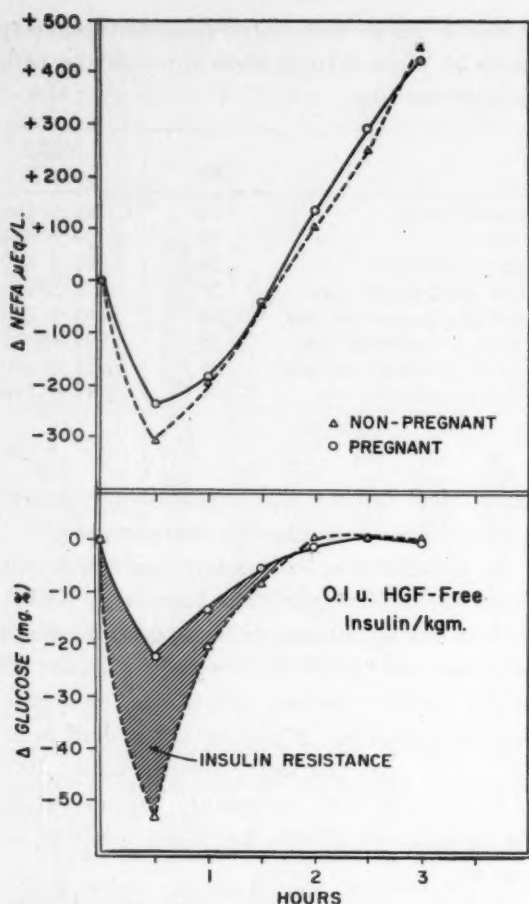


Fig. 4. Changes in NEFA and glucose concentration (Δ NEFA: Δ glucose) for normal pregnant and control subjects receiving 0.1 unit HGF-free insulin per kilogram body weight. Mean differences from pretest values are shown. The crosshatched area indicates the degree of insulin resistance developed in late pregnancy.

utilization may be differently affected with the resulting balance in favor of NEFA accumulation in peripheral plasma, the observed level or concentration not affording information concerning rates of turnover. From other studies, however, showing that increases in plasma NEFA occur with failure (diabetes) or attenuation (starvation) of carbohydrate utilization it is conceivable that the gestational increments may be related in some manner to the alterations in carbohydrate metabolism that we have previously described. These changes are those of insulin resistance⁸ which is readily demonstrable at least between 36 weeks and term in association with evidence of impaired peripheral

glucose utilization at this time.⁶ An additional factor may be the tendency to low normal fasting blood sugar levels in pregnancy that has been described by many observers⁶ and which may be related to decreased glucose-6-phosphatase activity of the liver.⁷ In consequence of this, it is possible, although direct evidence is not available, that decreased hepatic glucose release results in decreased availability of glucose to the peripheral tissues under fasting conditions. This combination of circumstances when considered in terms of our present understanding of the mechanism of NEFA control may be reflected by the gestational hyperlipidemia that we have described. The increase in NEFA concentration would thus represent a compensatory mechanism providing fat calories as in other situations where deficiencies in carbohydrate availability or utilization exist. Although these considerations may bear on the higher levels of nonesterified fatty acids under fasting conditions, our observations concerning NEFA changes following insulin or tolbutamide treatment suggest that the regulatory mechanisms for this lipid fraction are somewhat more complex than previously supposed.

It is apparent from our data that the changes in NEFA concentration in absolute values are equivalent for control and pregnant subjects despite significant resistance to insulin as evidenced by attenuated blood sugar and inorganic phosphate falls between 36 weeks and term. The latter observations are comparable to those we have previously reported.⁸ Evidently, the peripheral utilization of glucose in the fasting subject may be decreased as one aspect of insulin resistance with failure of corresponding effect on the concentration of nonesterified fatty acids. Thus, in pregnant subjects the effects of insulin on carbohydrate and lipid metabolism appear to dissociate, NEFA changes being unaltered despite obvious insulin resistance. The precise mechanism of this divergent metabolic activity is uncertain although unpublished data from our laboratory indicate that the changes in NEFA concentration are not necessarily simply and directly related to

glucose utilization. For example, a 25 gram intravenous glucose load produces significant hyperglycemia and hypophosphatemia in normal pregnant, puerperal, or nonpregnant subjects.⁹ It is surprising to find, however, in puerperal subjects that at this glucose dosage the plasma NEFA level is not usually significantly affected. On the other hand, for all subjects studied this amount of glucose completely inhibits NEFA rebound occurring after insulin administration and stabilizes the NEFA level at any given point in the evolution of the biphasic curve resulting from intravenous insulin. In fact, at this dosage, complete suppression of the NEFA response to insulin occurs in the early puerperium. Lactate is approximately 25 times as effective as glucose in producing the modifications of the NEFA response to insulin, possibly because of the proximity of this intermediate to acetyl co-A and the Krebs cycle. The failure to correlate the attenuated hypoglycemia and hypophosphatemia in pregnant subjects with comparable decreased NEFA falls becomes even more confusing when the diminished ability to produce lactate after administration of insulin in pregnancy is considered.¹⁰ Corresponding loss of NEFA response would be expected in this circumstance with decreased lactate production.

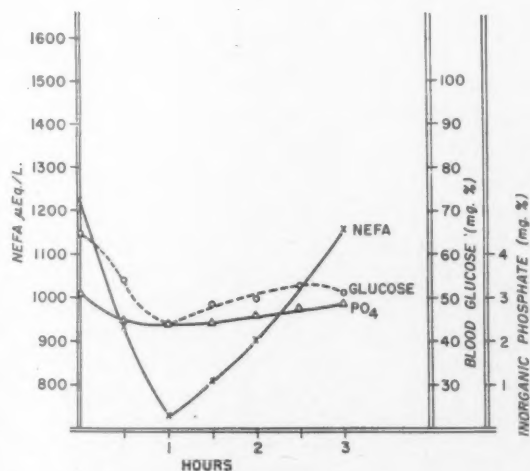


Fig. 5. Mean NEFA, glucose, and inorganic phosphate changes following administration of 20 mg. tolbutamide per kilogram body weight for 20 subjects between 36 and 40 weeks' gestation.

It is possible that the dissociation of hypoglycemia and NEFA response may be related to direct effects of insulin or tolbutamide on adipose tissue synthesis and release of the NEFA fraction as unique reactions that are not altered in gestation, despite obvious changes in carbohydrate utilization. The complexity of the factors involved in the partition of NEFA between depot fat, plasma transport of unesterified fatty acids, and tissue, as well as plasma triglyceride, is

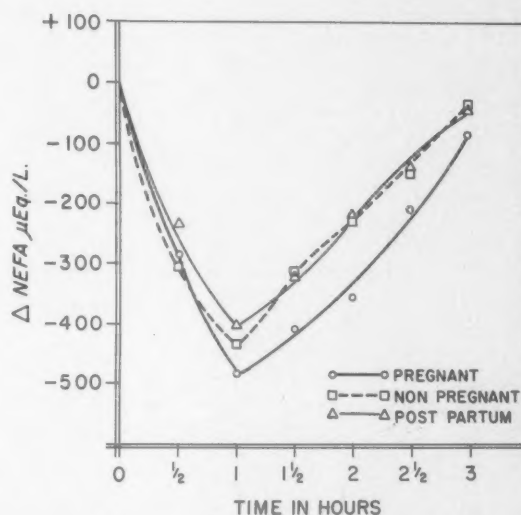


Fig. 6. Mean decrements for NEFA ($\mu\text{Eq/L}$) for pregnant, postpartum and control subjects receiving 20 mg. per kilogram tolbutamide.

indicated by a recent report of Laurell who stated that NEFA recycling was profoundly affected by glucose feeding in experimental animals. The particulars of lipid metabolism in pregnancy, as well as the precise interpretation of our observations, must await further isotope studies that will provide turnover rate data impossible to assess by the techniques we have employed in the present study. In conclusion, however, it seems that the pregnant woman is a metabolic curiosity by reason of her differential reactivity of NEFA, plasma inorganic phosphate, and glucose to hypoglycemic agents.

Summary

1. Significant increments in plasma non-esterified fatty acids occur between 36 weeks

and term. Whether the accumulation of fatty acid is due to increased rates of release from lipid depots or decreased utilization is not known. It is suggested that the elevated levels may be related to changes in carbohydrate utilization.

2. Differential reactivity to insulin and tolbutamide with respect to depression of NEFA concentration and hypoglycemia

have been observed in normal and toxemic pregnancy. Despite significant insulin resistance the NEFA response is unchanged.

3. The dissociation of NEFA reactivity from the hypoglycemia and hypophosphatemia resulting from insulin or tolbutamide may ultimately bear on the mechanism of action of these agents on lipid synthesis, utilization, and release.

REFERENCES

1. Bierman, E. L., Dole, V. P., and Roberts, T. N.: *Diabetes* 6: 475, 1957.
2. Bierman, E. L., Roberts, T. N., and Dole, V. P.: *Proc. Soc. Exper. Biol. & Med.* 95: 437, 1957.
3. Bierman, E. L., Schwartz, I. L., and Dole, V. P.: *Am. J. Physiol.* 191: 359, 1957.
4. Bragdon, J. H., and Gordon, R. S., Jr.: *J. Clin. Invest.* 37: 574, 1958.
5. Burt, R. L.: *Obst. & Gynec.* 15: 460, 1960.
6. Burt, R. L.: *Obst. & Gynec.* 4: 58, 1954.
7. Burt, R. L.: *AM. J. OBST. & GYNEC.* 77: 6, 1959.
8. Burt, R. L.: *Obst. & Gynec.* 7: 658, 1956.
9. Burt, R. L.: Unpublished data.
10. Burt, R. L., and Pulliam, R. P.: *Obst. & Gynec.* 14: 518, 1959.
11. Dole, V. P.: *J. Clin. Invest.* 35: 150, 1956.
12. Dole, V. P., Bierman, E. L., and Roberts, T. N.: *J. Clin. Invest.* 36: 884, 1957.
13. Gordon, R. S., Jr., and Cherkes, A.: *J. Clin. Invest.* 35: 206, 1956.
14. Gordon, R. S., Jr., Cherkes, A., and Gates, H.: *J. Clin. Invest.* 36: 810, 1957.
15. Havel, R. J., and Fredrickson, D. S.: *J. Clin. Invest.* 35: 1025, 1956.
16. Laurell, S.: *Acta physiol. scandinav.* 47: 218, 1959.

Discussion

DR. S. LEON ISRAEL, Philadelphia, Pennsylvania. This timely presentation, extending the essayist's prior work in the field of fat metabolism during pregnancy, draws our attention to the presently exciting subject of plasma lipids in various physiologic and pathologic states. This is a topic so full of challenging possibilities that it may, in Hamlet's descriptive words, "Confound the ignorant; and amaze, indeed, the very faculties of eyes and ears."

Ever since 1934, when Lee and Schaffer observed that pituitary growth hormone exerts profound effects on lipid metabolism, it has been appreciated that fatty acids have a major role in metabolic homeostasis. The fact that purified preparations of growth hormone effect mobilization of fat from storage depots to the liver emphasizes the relation of that hormone to lipid metabolism and underscores the importance of NEFA. Moreover, such fatty acids—mostly palmitic, stearic, and oleic—are also rapidly mobilized by at least two additional stimuli, other than growth hormone, fasting or starvation and epinephrine-norepinephrine secretion. Studies of the rise in plasma lipids occasioned by either starvation or adrenal secretions indicate that the pituitary gland is not required for such a re-

sponse and suggest that peripheral factors are in control of this phenomenon.¹ Furthermore, the ready availability of glucose or the presence of insulin reverses the tide of plasma lipids—a physiologic reaction that brings into focus, as re-emphasized for us today, the close relationship between fat and carbohydrate metabolism.

Dr. Burt's prior demonstration of the marked increase in plasma NEFA during the latter part of pregnancy now takes on a new dimension. Today, he points out that the pregnant woman is a metabolic curiosity "in that she shows a clear dissociation of the effects of insulin on carbohydrate and lipid metabolism," a dissociation that may be the permissive factor in the hyperlipidemia occurring at term. Such a provocative finding leads, quite naturally, to speculation concerning the teleologic meaning of the heightened plasma lipids prior to labor. The augmentation may perhaps be related to 3 recent additional observations involving NEFA—the maternal-fetal lipid ratio, the lipidemia of stress, and the long-chain fatty acids purported to evoke myometrial contractions.

Although the fetus does not share in the maternal lipidemia near term, a fact consistent with the belief that the fetus subsists mainly on carbohydrate metabolism, workers in Page's laboratory

have found that a rapid shift from a carbohydrate type of energy to the fat-depot mobilization kind of energy occurs soon after birth of the baby. The early neonatal period is apparently signalized by a measurable elevation of plasma lipids.² This may be related to "an increase in sympathetic nervous activity" in the newborn, for Havel and Goldfien have shown that anxiety or discomfort in human beings, as well as in dogs, increases the quantity of circulating lipids.³ They have in fact proposed the concept that "the sympathetic nervous system exerts a tonic reaction on the mobilization of fatty acids from adipose tissue which may be altered by central stimuli as well as by hormonal factors." Could such sympathetic activity also be a rational explanation for hyperlipidemia of term pregnancy?

More arresting, perhaps, is the discovery by Pickles of a myometrium-stimulating substance in human endometrium, identified by him as a complex of long-chain fatty acids.⁴ Is it possible that this lipid stimulant of myometrial contractions, shown by Pickles to be present in menstrual fluid as well as in systemic blood during menstruation, is in some way related to the subject under discussion? Could the need for such a contractile agent, fantastic as it may seem, be the reason for the prelabor hyperlipidemia of pregnancy?

This discussion of NEFA has been limited to the obstetric confines set by Dr. Burt's theme. The temptation to relate this subject to gynecology, more especially to the projected relationship between the lipidemia of both castrated and postmenopausal women and the manifestations of atherosclerosis, has been resisted. Such talk would lead us far afield to the area of coronary heart disease and oophorectomy.⁵

Finally, when a neophyte—attempting to follow one of the admonitions of the Apocrypha, "Be not ignorant of anything in a great matter or a small"—reads in this field, he is baffled by the array of apparently interchangeable alphabetical abbreviations presently in use to designate a portion of the plasma lipids. A team of linguists should attack the problem posed by the seemingly synonymous terms, unesterified fatty acids (UFA), nonesterified fatty acids (NEFA), and free fatty acids (FFA). The use of abbreviated titles, more especially strange and barbaric ones, gives any subject status. It is thus endowed with an aura of widespread acceptance, even to the point of creating guilt in the mind of the unknowledgeable reader because of his "Gothic

ignorance." There is really no reason for such a profusion of terms, an excess that results in too many synonyms and heightens the confusion. Our essayist has identified himself as an "NEFA man." May I conclude this discussion by asking Dr. Burt what determined his choice. Would he, for instance, be offended to be grouped with the "UFA and FFA men"?

REFERENCES

1. Knobil, E., and Greep, R. O.: In Pincus, Gregory, editor: *Recent Progress in Hormone Research*, ed. 15, New York, 1959, Academic Press, Inc., p. 1.
2. Van Duyne, C. M., and Havel, R. J.: *Proc. Soc. Exper. Biol. & Med.* 102: 599, 1959.
3. Havel, R. J., and Goldfien, A.: *J. Lipid Res.* 1: 102, 1959.
4. Pickles, V. R.: *J. Endocrinol.* 19: 150, 1959.
5. Robinson, R. W., Higano, N., and Cohen, W. D.: *A. M. A. Arch. Int. Med.* 104: 908, 1959.

DR. BURT (Closing). No, I would not be adverse to being called a "UFA man," an "FFA man," or an "ABFA man," which denotes albumin-bound fatty acid. Actually, we call this NEFA because we started out with that notation 4 years ago when we inevitably progressed from a carbohydrate study into lipids. This was a natural evolution in studying metabolism. At that time Dole had just described his method and there were only two camps—NEFA and UFA—but now it is fantastic. We will stay with the NEFA notation because these compounds are nonesterified in contrast to fatty acids which occur in various combinations in other compounds.

As Dr. Israel has pointed out, there are many factors that will influence NEFA—epinephrine, pituitary growth hormone, stress, and so on. Precisely how these factors influence NEFA we do not know. We regard NEFA in terms of what seems to be consistent with our philosophy of carbohydrate utilization in pregnancy. Apparently there are gestational changes that are deleterious to the utilization of carbohydrate. From clinical experience aggravation of diabetes occurs in pregnancy. Transient diabetes in pregnancy is well known, and insulin resistance can be demonstrated. When insulin is not available or when resistance to its action occurs, hyperlipidemia should develop. We are now concerned with describing more of this chemical morphology in gestation. We want to find out what happens and why.

End results in adenocarcinoma of the endometrium managed by preoperative irradiation

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ALTHOUGH carcinoma of the endometrium has been regarded as having the best prognosis of all gynecologic cancers, reports in the literature and the results, as summarized in the Eleventh Annual Report on the Results of Treatment in Carcinoma of the Uterus, indicate clearly that our management of this disease leaves much to be desired.¹⁻⁵ Because of good results in selected groups of patients some of us have become overly optimistic about the outlook for the patient with corpus cancer. We tend to forget that these results are limited usually to the favorable cases and that these comprise considerably less than one half of the patients seen in most clinics.

The attitude of optimism in our own clinic has reflected this thinking. We have been aware of the rather low over-all survival rate, but much of our thinking, planning, and talking has centered around the diagnosis, treatment, and end results in the most favorable cases.

I suspect that this attitude has been shared

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by many other clinics since it is agreed generally that early diagnosis and meticulous individual attention to the favorable case is the one means of improving our results in the treatment of this disease.⁶

The present study was undertaken in order to re-evaluate the results of the treatment of endometrial carcinoma in our own institution and especially to present a clear view of the factors responsible for these results.

Material

The material available (Table I) for 5 year evaluation consists of 297 patients with endometrial carcinoma who were registered in the Pelvic Malignancy Clinic of the Jefferson Medical College Hospital between Sept. 1, 1921, and Dec. 31, 1954. This includes all of the patients on the ward and clinic services and all of the patients on the private service of those members of the staff who have been intimately concerned with the operation of this clinic since it was organized originally by Dr. Lewis C. Scheffey.⁷⁻¹⁴

One hundred seventy-five of the 297 cases were reported by Dr. Scheffey in 1952. They have been restudied and will be contrasted with 122 new cases that were treated during

the years 1947 through 1954. All of the 297 patients were treated during the years when Dr. Scheffey was the head of the department and the active director of the Pelvic Malignancy Clinic.

One hundred twenty-three (42 per cent) were ward patients, and 174 (58 per cent) were on the private service. The follow-up has been complete to date except for 2 private patients who have not been seen for 2 years but who are not yet regarded as lost to follow-up.

Results

One hundred ninety-three of the 297 patients (Table II) survived for 5 or more years, an absolute survival of 65 per cent. If we eliminate 8 patients who were treated elsewhere primarily, 4 of whom survived, and 5 patients who were untreated, there remain 189 survivors in 284 treated patients, or a relative survival of 67 per cent (Table III).

Although no striking improvement can be noted when the 5 year results after 1946 are compared with the previous ones, the record in recent years indicates considerable improvement when compared with the 39 and 55 per cent of survivals reported previously by Dr. Scheffey, who evaluated some of the cases in 1943 and 1948, respectively. We believe that this progressive improvement has been due to an increasing number of favorable cases, but it is recognized that improved operative technique and many other factors probably influence the results. It is difficult to be specific about this because of the many uncertain factors. This is reflected in the wide variety of methods by which these patients have been treated. Eight different methods have resulted in groups of cases most of which are too small to be of significance in evaluating the results of therapy.

The choice of these therapeutic procedures has been influenced largely by the extent of the disease, the physical condition of the patient, sometimes her lack of cooperation, and the clinical judgment of the gynecologist.

For many years we have preferred pre-

liminary irradiation with intrauterine radium, applied usually at the time of the diagnostic curettage, and followed in 6 weeks by total abdominal hysterectomy and bilateral salpingo-oophorectomy. The extent of the disease too often has dictated a less satisfactory plan. Sometimes the condition of the patient or our failure to make an accurate primary diagnosis has prevented its use. The presence of uterine myomas sometimes has been a deciding factor. The end result has been that approximately 60 per cent of our patients have received some form of treatment other than our preferred method.

A brief review of these various groups of treated patients reveals, however, that there were a considerable number of survivors in all categories except where exploratory incision or palliative x-ray therapy alone was the only procedure which could be carried out.

Adequate operation alone. (Table IV.) Operation without irradiation has played a very small part in the treatment of endome-

Table I. Record of patients seen and 5 year follow-up

Years	Pa- tients	Treated	Ward	Private	Follow- up
1921-1946	175	168	73	102	175
1947-1954	122	116	50	72	122
1921-1954	297	284	123	174	297

Table II. Five-year results of all patients seen

Years	Patients	Survivors	Per cent
1921-1946	175	110	63
1947-1954	122	83	68
1921-1954	297	193	65

Table III. Five-year results in relation to all patients treated

Years	Patients	Survivors	Per cent
1921-1946	168	107	64
1947-1954	116	82	71
1921-1954	284	189	67

trial cancer in our institution because we have been convinced that preliminary devitalization of the tumor by irradiation is a preferable method of treatment. Only 20 patients have been treated by adequate operation alone (total abdominal hysterectomy and bilateral salpingo-oophorectomy). In 13 of these, uterine myomas either interfered with the proper application of intrauterine radium or prevented detection of a small cancer until the uterus had been removed. Four patients who had been treated previously with radium for benign bleeding and one who had a benign ovarian cyst were operated upon primarily also. In 2 others, who were treated prior to 1930, the reason for relying upon operation alone was not stated.

There was one postoperative death which has been reported previously. Four patients died of recurrent disease in less than 2 years after operation. One of these had recurrence in the vaginal vault as did one other who died 9 years after operation. Two are living and well 6 and 8 years after operation, and one died of intercurrent disease 5½ years later. Eleven patients survived more than 10 years. Two of these have died of intercurrent disease.

Seven of the survivors had tumors of low-grade malignancy and 8 had high-grade lesions. Three of those who died within 2 years had intermediate grade and 2 had anaplastic lesions. The cases in this category are so few that the results are not of statistical significance.

Inadequate operation alone. In 5 patients incomplete operation was the sole treatment. There were two postoperative deaths: one from peritonitis (reported previously) and one from adynamic ileus in a patient with far-advanced disease. Two patients died within one year, and one lived for 4½ years.

Radium alone. (Table V.) Forty-six patients were treated solely with radium. Subsequent operation was not performed because most of these women were thought to represent very poor risks, usually because of cardiovascular disease, diabetes, extreme obesity, advanced age, or a combination of

Table IV. Five-year results among patients treated by adequate operation alone

Years	Patients	Survivors	Per cent
1921-1946	15	10*	66.6
1947-1954	5	5	100.0
1921-1954	20	15	75.0

*Postoperative deaths, 1—1929.

Table V. Five-year results in patients treated by radium alone

Years	Patients	Survivors	Per cent
1921-1946	32	18	56.2
1947-1954	14	10	71.4
1921-1954	46	28	60.8

these contraindications. Six patients refused operation and in 7 the radium was given to control hemorrhage in advanced disease.

Previous to 1947 all patients were treated by the tandem method, with use of two capsules each of 2 cm. active length containing 50 mg. of radium screened with 1.5 mm. of platinum and enclosed in a rubber tube of 2 mm. thickness. Since 1947, multiple small sources of radium have been available and a few of the 14 patients were treated by this method.

Although the dose was standardized at 4,500 to 5,000 mg. hr. exposure, it actually varied rather widely according to the size of the uterus and the clinical judgment of the operator. Eight patients received less than 3,000 mg. hr. and 5 of them died within 2 years and 3 survived. Two of these died of recurrent disease after 8 years and one is well 25 years after treatment for a tumor of low-grade malignancy. Three of 7 patients who received approximately 3,600 mg. hr. have survived more than 5 years. Nineteen patients received approximately 5,000 mg. hr. and 9 of these survived more than 5 years. Of 12 who received 6,000 mg. hr. or more, 9 survived more than 5 years. All of the 12 received irradiation therapy in divided doses.

Fourteen patients, or one half of the sur-

vivors, had low-grade malignancy and 3 had adenoacanthomas, 10 had intermediate-grade tumors and one had anaplastic carcinoma. Among those who died, 4 had low-grade, 7 intermediate-grade, 5 high-grade malignancy, and one adenoacanthoma; one slide was not available for grading.

From this experience one might infer that radium alone may be a satisfactory method of treatment for some poor-risk patients. It would seem that the results might be influenced not only by the extent of the disease but by the grade of malignancy and the intensity of irradiation.

Since 61 per cent of these poor-risk patients lived for 5 years or longer, one must question the clinical judgment in classifying them as representing poor surgical risks. However, such criticism must be tempered by the knowledge that 8 patients died of intercurrent disease, usually cardiovascular lesions, between 5 and 10 years after treatment and 6 died of intercurrent disease after 10 years. Four died of cancer during the second 5 year period. Ten are living and well more than 10 years after therapy.

X-ray alone. This was the method of treatment in only 5 patients. All had advanced disease and none survived more than 3 years.

Table VI. Five-year results in patients treated by radium and x-ray

Years	Patients	Survivors	Per cent
1921-1946	37	17	45.9
1947-1954	9	4	44.4
1921-1954	46	21	45.6

Table VII. Five-year results in patients treated by inadequate operation plus irradiation

Years	Patients	Survivors	Per cent
1921-1946	12	8	66.6
1947-1954	3	2	66.6
1921-1954	15	10	66.6

Radium and x-ray. (Table VI.) In this category, the patients either were poor operative risks or they had advanced disease. A few refused operation. They were satisfactory subjects for x-ray therapy, and this was added either because the disease was definitely advanced or the operator thought that the additional therapy would safeguard the patient.

Factors employed in the x-ray therapy have been recorded previously. A total of 1,600 to 2,400 r was usually given to two anterior and two posterior pelvic portals. Seventeen patients received less than 4,000 mg. hr. of radium. Seven of these survived for more than 5 years. Of 12 who received 4,000 to 4,500 mg. hr., 8 survived for more than 5 years, and 6 of 17 who received 5,000 mg. hr. or more survived for more than 5 years.

The various grades of malignancy were almost equally divided among the survivors and those who died: low grade 8 to 7; intermediate grade 9 to 11; and high grade 3 to 5. There were two adenoacanthomas among those who died. In one patient who lived for 8 years the slide was not available for grading.

Eleven of the 21 5 year survivors lived from 5 to 10 years but 9 of these have died; 2 are living. Ten additional patients lived for 10 or more years and 3 of them are still living. Three of the 10 died of intercurrent disease, 2 died of recurrent cancer, and in 2 the cause of death is not known.

Inadequate operation plus irradiation. (Table VII.) This small group of patients was treated with x-ray or radium in addition to incomplete operation. Some had advanced disease. In 8 patients, carcinoma was encountered unexpectedly after supravaginal hysterectomy for uterine myomas. One patient was very obese. Two were treated by vaginal hysterectomy without salpingo-oophorectomy. One of these had preliminary intrauterine radium and the other received postoperative x-ray. One patient had an incomplete operative procedure 5 years after the initial treatment with 2,400 mg. hr. of radium.

Table VIII. Five-year results in patients treated by adequate operation plus irradiation (unplanned techniques)

Years	Patients	Survivors	Per cent
1921-1946	19	10	53
1947-1954	8	1	13
1921-1954	27	11	41

Table IX. Five-year results in patients treated by preliminary radium plus adequate operation (planned technique)

Years	Patients	Survivors	Per cent
1921-1946	48	44	91
1947-1954	72	60	83
1921-1954	120	104	87

The 8 patients who had supravaginal hysterectomy are among the survivors. The 2 patients who had a vaginal hysterectomy alone after radium 5 years previously survived for 6 years.

Five survivors had low-grade tumors; one was an adenoacanthoma, 3 were intermediate grade, and one was not graded. Three patients died of carcinoma between the fifth and the tenth year after treatment. One died of heart disease and one is living with carcinoma probably present 8 years after treatment. Five of the 10 survivors have lived 10 or more years. Two of these subsequently died of heart disease.

Adequate operation plus irradiation (not planned). (Table VIII.) All of these patients had a total abdominal hysterectomy with bilateral salpingo-oophorectomy plus preoperative radium and/or postoperative x-ray treatment. In 9 patients radium was given as a definitive treatment and operation was performed when symptoms recurred 1 to 5 years later. Postoperative x-ray treatment was given when malignancy was encountered unexpectedly, and a few patients received both radium and x-ray therapy postoperatively. Five patients were treated by our planned method, and x-ray therapy was added when extrauterine disease was en-

countered at operation. All of these died within 1 year.

Three patients died of recurrent cancer between the fifth and the tenth year after treatment. Eight of the 11 survivors lived for 10 or more years, but 3 of these now have died of intercurrent disease.

Five of the 11 survivors had low-grade and 6 had intermediate-grade tumors. Low-grade tumors occurred in 5, intermediate-grade in 8, and high-grade in 3 of the patients who lived less than 5 years.

Preliminary radium plus adequate operation (planned technique). (Table IX.) These were the most favorable cases. In each instance the carcinoma was limited to the uterus and all patients were satisfactory subjects for preliminary intrauterine radium therapy followed in 6 weeks by total abdominal hysterectomy and bilateral salpingo-oophorectomy after preliminary suture closure of the cervix and tubes. We have referred to this as our planned technique or our preferred method of treating corpus cancer. X-ray therapy has not been utilized in any of these patients. (In 5 patients who were originally thought to be satisfactory for this therapy, the carcinoma was found subsequently to extend beyond the uterus. They were given x-ray therapy in addition and are included in the previous category.) (Table VIII.)

The radium was applied usually at the time of the diagnostic curettage in the form of one or two 50 mg. capsules in tandem screened by 1.5 mm. of platinum as described previously. During the period 1947 to 1954, half of the 72 patients were treated by packing the uterine cavity with twenty to twenty-five 5 mg. capsules of radium screened with 1 mm. of platinum with the exposure ranging from 5,000 to 6,000 mg. hr.

Although the optimal irradiation exposure was fixed at 4,500 to 5,000 mg. hr. with the tandem technique the dose has varied considerably, especially during the period before 1947. Thirty patients (25 per cent) received 3,600 mg. hr. of radium or less. Twenty-eight of these (94.4 per cent) have survived. All of the others (84 patients) re-

ceived 4,500 mg. hr. or more, but only 12 received more than 6,000 mg. hr. Seventy-six of these, or 83 per cent, have survived. When we consider survival in relation to the method of irradiation, we find that 26 (72.5 per cent) of 36 patients treated with the multiple capsule technique and 74 (88 per cent) of 84 treated with the tandem method have survived.

Thirty-three survivors are now in their second 5 year posttreatment period. One of them has died of recurrent disease and one succumbed to a second cancer in the colon. Seventy-one patients (59 per cent) have survived for 10 or more years.

The histologic grade of malignancy is undoubtedly related to survival. There were 45 low-grade, 63 intermediate-grade, and 10 high-grade tumors. The number of survivors in these groups were 44, 52, and 8, respectively.

The effectiveness of the irradiation therapy in these groups can be evaluated in part by the presence or absence of residual carcinoma (Table X) in the uterus removed 6 weeks following the therapy. Our specimens have not been studied by serial section, as has been done by Schmitz and others. The incidence of residual carcinoma reported here is dependent upon the routine examination of the specimen in the general laboratory of clinical pathology where several histologic sections were examined routinely. Contrary to our previous reports, which were based upon incomplete evaluation of our material, there is little difference in the survival rate in the groups with or without residual cancer.

The over-all results in our planned therapy have been influenced also by the preponderance of private patients (Table XI) in whom the survivals have been greater than the ward patients who often are less favorable subjects.

Comments

Our results in the treatment of endometrial carcinoma are essentially the same as those reported by other clinics. There has been slow but progressive improvement over

the past 25 years. This would seem to be due largely to the increase in favorable cases. Among the 175 patients treated prior to 1947, there were only 48 or 27.4 per cent who were treated by our preferred technique, while during the years 1947 to 1954 there were 72 or 59 per cent of such cases among the 122 patients treated (Table IX).

It is obvious, however, that these total results were influenced by many other factors in addition to the extent of the disease. In many instances the general physical condition of the patient and sometimes her lack of cooperation resulted in treatment that was not ideal. Sometimes associated pelvic lesions influenced this decision. Tables XII and XIII show a striking difference between the results among private and ward patients.

The grade of malignancy (Table XIV) has exerted an influence on these results since the percentage of survivors is definitely higher in the patients with low-grade malignancy. Although the number of patients with high-grade malignancy is small, the low rate of survival would seem to be significant.

It is difficult to evaluate accurately the influence of the intrauterine irradiation on the survival. However, its efficacy in the treatment of corpus cancer is clearly demonstrated by the survival of 28 of 46 patients

Table X. Relation of survival to finding of residual carcinoma after planned radiotherapy

	Removed uterus	Survivors	Per cent
No residual	61	55	90.2
Residual	59	49	83.0
Total	120	104	86.7

Table XI. Five-year results in ward and private patients after planned therapy

	Planned	Survivors	Per cent
Ward	33	25	76
Private	87	79	91
Total	120	104	87

Table XII. Five-year results in all ward and private patients seen

	<i>Patients</i>	<i>Survivors</i>	<i>Per cent</i>
Ward	123	63	51.2
Private	174	130	74.7
Total	297	193	64.9

Table XIII. Incidence of planned therapy among ward and private patients

	<i>Patients</i>	<i>Planned</i>	<i>Per cent</i>
Ward	123	33	26.8
Private	174	87	50.0
Total	297	120	40.4

Table XIV. Five-year results in relation to grade of malignancy

<i>Grade</i>	<i>Patients</i>	<i>Survivors</i>	<i>Per cent</i>
Low	93	77	83
Intermediate	139	89	64
High	33	13	39
Adenoacanthoma	12	8	67
Not graded	7	2	--
Total	284	189	67

who were treated by radium alone. In order to be effective, however, intrauterine radium must deliver a cancerocidal dose (minimum of 6,000 to 8,000 r) to all of the cancer-bearing tissue. Our therapy has probably fallen short of this objective in some cases.

It has been estimated that our tandem application delivered approximately 370 r per hour at a distance of 1 cm. from the center of the tube. With the 5,000 mg. hr. application, this would amount to 18,500 r. However, when one considers the rapid fall-off according to the inverse square law, this dose decreases to 145 r at a distance of 2 cm. or 7,250 r by the 5,000 mg. hr. standard, and at 3 cm. from the center of the tube only 70 r are delivered per hour or 3,500 r for the 5,000 mg. hr. application.

It is obvious that this method may be very effective in the small uterus. It is equally obvious that its efficiency decreases rapidly when smaller doses are used or when the uterus is enlarged or distorted.

The multiple source technique which was used in some of these patients, and which we now use routinely unless the uterus is small, should supply a more uniform irradiation to the entire endometrium if properly applied and maintained. However, calibration of the tumor dose from multiple sources is difficult and at present we do not know the exact amount of irradiation that is being delivered to the endometrium by the 6,000 mg. hr. exposure by this technique. Although the irradiation is delivered more uniformly, it is our impression that the intensity at any point is less than with the tandem application. The 36 favorable cases in which treatment by this method was used are too few to warrant an opinion concerning the results. However, it is interesting to note that although there was no residual tumor in 24 of these uterine specimens, only 66 per cent of the patients survived, as compared to 86 per cent survival in all 120 patients treated by our preferred method. This would seem to indicate that the 6,000 mg. hr. application that has been our standard dose with this technique is also inadequate in some cases.

Table XV. Summary of five-year results in different categories

<i>Treatment</i>	<i>Patients</i>	<i>Survivors</i>	<i>Per cent</i>
Adequate operation	20	15	75.0
Inadequate operation	5	0	0.0
Radium alone	46	28	60.8
X-ray alone	5	0	0.0
Radium plus x-ray	46	21	45.6
Inadequate operation plus irradiation	15	10	66.6
Adequate operation plus irradiation (not planned)	27	11	40.7
Radium plus operation (planned)	120	104	86.6
Total patients treated	284	189	66.5
Treated elsewhere	8	4	50.0
Untreated	5	0	0.0
Total number of patients	297	193	64.9

The radium dosage administered in our planned therapy must be judged in the light of its intended objective. It has been used on the assumption that it would devitalize but not destroy the carcinoma and thus prevent manipulative spread and subsequent local recurrence of the lesion. Since its use has resulted in complete destruction of the cancer within the uterus in more than one half of the cases and since there have been only two local recurrences in the vaginal vault, we believe its value has been demonstrated clearly. Harmful effects of the radium have been limited to a few cases of mild proctitis.

This experience has convinced us that intrauterine radium is a valuable adjunct in the treatment of fundal cancer. Its value undoubtedly is directly related to the effectiveness of the method used. This was emphasized by the late Herbert E. Schmitz before this Society last year when he stated that "failures with inadequate therapy should not be used to discredit this technique."¹⁶ Our experience leads us to believe that improved results may be expected if we were to follow Dr. Schmitz's lead and develop safe irradiation techniques that will deliver more intense irradiation with the object of completely destroying the tumor whenever possible. To this end, many of us who are not highly trained in the minute details of irradiation techniques would do well to seek the aid and cooperation of the trained radiation therapist. His skill in the minutiae of irradiation therapeutic techniques, combined

with the experience of the gynecologist, should aid in attaining this objective. If improved irradiation methods can increase the salvage of patients with corpus cancer even a small per cent beyond that which may be expected from operation alone, our efforts in that direction will be very much worth while.

Summary

1. Table XV presents a summary of the 5 year results in 297 patients seen during the 34 years, 1921 to 1954.

2. Irradiation, especially with intrauterine radium, has played a prominent part in the therapy. In operable cases it has been used primarily to devitalize the carcinoma and thereby prevent manipulative spread and local recurrence.

3. The preferred method of treatment has been intrauterine radium followed in 6 weeks by total abdominal hysterectomy and bilateral salpingo-oophorectomy. Sixty per cent of the patients were treated by less satisfactory methods, usually because the carcinoma was advanced or the patient was a poor operative risk.

We wish to thank Hyman Menduke, Ph.D., Associate Professor of Biostatistics, for his help in the statistical evaluation of our results and Simon Kramer, M.B., Professor of Radiology, for his aid in the preparation of the discussion of radiation factors. During the latter part of the period evaluated in this report, Dr. Theodore Eberhard was the radiotherapist.

REFERENCES

1. Annual Report on the Results of Treatment in Carcinoma of the Uterus, Stockholm, 1958, Norstedt and Soner, vol. 11.
2. Henriksen, E., and Murrietta, T.: *West. J. Surg.* 58: 331, 1950.
3. Javert, C. T.: *Obst. & Gynec.* 12: 556, 1958.
4. Kottmeier, H. L.: *AM. J. OBST. & GYNEC.* 78: 1127, 1959.
5. Nugent, F. B., and Gluckert, J. C.: *Obst. & Gynec.* 7: 406, 1956.
6. Miller, N. F.: *Obst. & Gynec.* 15: 579, 1960.
7. Scheffey, L. C., Thudium, W. J., and Farrell, D. M.: *AM. J. OBST. & GYNEC.* 46: 786, 1943.
8. Scheffey, L. C.: *S. Clin. North America* 25: 1262, 1945.
9. Scheffey, L. C., Thudium, W. J., Farrell, D. M., and Hahn, G. A.: *AM. J. OBST. & GYNEC.* 52: 529, 1946.
10. Scheffey, L. C., and Lang, W. R.: *S. Clin. North America* 28: 1425, 1948.
11. Scheffey, L. C.: *Pennsylvania M. J.* 52: 944, 1949.
12. Scheffey, L. C.: *South. M. J.* 42: 44, 1949.
13. Scheffey, L. C., and Lang, W. R.: *S. Clin. North America* 32: 1729, 1952.
14. Scheffey, L. C.: Discussion of Schmitz, Smith, and Gajewski.¹⁵

15. Schmitz, H., Smith, C. J., and Gajewski, C. J.: *AM. J. OBST. & GYNEC.* 64: 952, 1952.
16. Schmitz, H. E., Smith, C. J., and Fetherston, W. C.: *AM. J. OBST. & GYNEC.* 78: 1048, 1959.
17. Beecham, C. T.: *AM. J. OBST. & GYNEC.* 10: 230, 1957.
18. Sandberg, E. C., and McClennan, C. E.: *Obst. & Gynec.* 9: 670, 1957.
19. Gusberg, S. B.: Discussion of Schmitz, Smith, and Fetherston.¹⁶

Discussion

DR. CARL T. JAVERT, New York, New York. Dr. John Montgomery has presented the Philadelphia story of end results following the preoperative, intrauterine application of radium for endometrial cancer over a 40 year period. A 5 year absolute survival rate of 65 per cent was obtained. His series of 297 cases go back to 1921. That only 20 patients had primary operation either attests a high degree of diagnostic accuracy or the conventional habit of inserting the radium while waiting for a "rush" or "6 hour" pathologic report. This practice has resulted in the widespread use of radium for benign as well as malignant diseases of the endometrium. As a result many of his cases of cancer are treated with a single tandem dosage of radium which we realize today is inadequate.

Even so, Dr. Montgomery has shown that cancer could no longer be demonstrated in the uterus after radium application in many of these cases. Those of us employing primary operation have been also amazed at the absence of residual cancer following simple curettage. In such cases, there are superficial lesions. Prognosis should be good under these circumstances, since the younger lesions have had less time to invade the uterus and to metastasize. Is Dr. Montgomery able to state in how many cases there was a positive diagnosis of cancer before definitive radium therapy was instituted?

Can Dr. Montgomery tell us in how many cases of endometrial cancer had there been treatment years previously with radium for benign disease? Nugent, of Reading, who follows the practices of nearby Philadelphia, reported an incidence of 6.1 per cent. At Woman's Hospital in New York we have noted an incidence of 7.8 per cent. Does Dr. Montgomery still advocate the use of radium to treat benign bleeding?

Some years ago I developed with Dr. Karl Hoffmann a surgical-pathological staging for endometrial cancer which included lymphadenectomy for prognosis only. Positive nodes were found in 15 per cent of the cases. The prognosis in these patients was poor. If the nodes were negative, they did not need to come out except

to establish this fact for prognostic purposes. If they were positive, postoperative x-ray irradiation was employed. One salient fact was established, and it was the tendency of endometrial cancer to metastasize to the vagina and liver in patients with positive nodes. As a result, I have moved cases with vaginal metastases from Stage II to Stage IV in our Pathologic Classification.

When the endometrial cancer is limited to the uterus, the results after primary operation and postoperative x-ray, as reported by R. Gordon Douglas and myself, were as good as those for operation following intracavitary radium as reported by John Montgomery today. When the disease has gone beyond the uterus the results have been poor either with primary operation and x-ray or with radium followed by operation. Advanced cases do poorly with either modality of treatment. Perhaps in these, exenteration has a place. There are many reports claiming advantages for preoperative use of radium without regard to the pathologic stage of the disease, which after all is the time-honored yardstick for evaluating results of therapy for cancer of the breast, lip, penis, etc. Could Dr. Montgomery tell us how many of his patients had positive nodes?

Moreover, could the essayist tell us whether the incidence of Stage 0 and Stage I cases has increased in Philadelphia as we have seen it increase in New York? This trend will have a salubrious effect on the survival rates per se, regardless of the therapy employed. Cytology has been credited with the detection of more early cases. Such programs will salvage more patients than extended surgical and radiation techniques. They have been credited by the American Cancer Society with the lowering of mortality rates in uterine cancer in recent years.

Finally, let me make a plea for an unhurried, pretherapeutic diagnosis of endometrial cancer before operation is employed or before the application of intrauterine radium. The importance of this point is illustrated by the case of a patient recently treated by a member of our courtesy staff. A large amount of endometrial tissue was

obtained by curettage. The uterine cavity was packed with five 50 mg. capsules of radium, by means of the approved Heyman technique, and two 25 mg. capsules in the vaginal fornices. Dosimeters were placed in the bladder and rectum. After 6 hours a pathologic report of "benign endometrial hyperplasia" was obtained.

Would it not have been wiser to have had an accurate diagnosis before exposing the patient, the doctor, the resident, the nurse, the anesthetist and several recovery room personnel and other patients to this large dose of radium for a benign disease? Dr. Leonard Liegner, our radiotherapist, has provided an accounting of the radiation exposure in this case.

The dosage delivered to the patient and the dosage received by the doctors and nurses during administration of 100 mg. of radium are as follows: patient, 50,000 mr.; doctors and nurses at 1 meter receive 8.4 mr. per hr.; at 50 cm., 34.0 mr. per hr.; at 25 cm., 135.0 mr. per hr.; the patient's roommates at 1 meter receive 8.4 mr. per hr.

Evaluation of the dosage based on present-day knowledge is as follows: (a) doctors and nurses are allowed 100 mr. per week; therefore, there is a possibility that in a *single* administration of radium the doctors and nurses received that allowable quota; (b) the general public is allowed 10 mr. per week; therefore, there is a possibility that the patient's roommates exceeded by a factor of 6 *times* their allowable quota; and (c) the patient with a noncancerous condition is considered "general public"; therefore, the patient in question received a dosage far in excess of permissible amounts by any standard.

A study of 600 cases at Woman's Hospital, where radium has been employed since 1919 gave a 5 year survival rate of 55 per cent as compared with Dr. Montgomery's rate of 65 per cent. Study of another series of 600 cases at New York Hospital where primary operation has been the procedure of choice revealed a 5 year survival rate of 65 per cent. This experience, together with observations made in the pathology laboratory over a 15 year period, when hundreds of specimens were studied, have convinced me of two things: (1) the pathologic stage is the most important yardstick with which to evaluate results of therapy, and (2) primary operation gives as good results as radium followed by operation. This can be seen by comparison of end results at New York Hospital, the Woman's Hospital, and the Jefferson Hospital.

The value of preoperative radium in preventing vaginal metastases remains unproved. Such cases show advanced occult disease and belong in Stage IV. Many of them represent spread of malignant adenoacanthoma, as shown by Way and myself. Only when a preoperative diagnosis is made and planned adequate therapy is employed can the superiority of preoperative use of radium be established. Moreover, periodic calibration of the radium is essential from time to time to make sure the capsules are intact and that some of the radium has not escaped. I would like to ask Dr. Montgomery the most embarrassing question of all: How long ago was the radium calibrated at Jefferson Hospital? This may explain why some of the patients did not do as well as was expected.

DR. SAUL B. GUSBERG, New York, New York.
I wish to make only two relatively minor points about this excellent presentation by Dr. Montgomery.

One cannot always evaluate grouped 5 year results in a meaningful way in a disease that occasionally has low malignancy. I would like to cite the recent case of a patient who had a dilatation and curettage *only* for carcinoma of the endometrium 6 years prior to presenting herself again. She had had no treatment in the interim and yet the disease was still localized. So I would say (1) that one must inspect very carefully the biologic grading and vitality of the tumor before estimating the result of treatment, and (2) confinement to the uterus is a relatively poor criterion for staging carcinoma of the corpus.

Here is the staging we have found useful. I do not wish to be repetitious about this for I reported on it to you last year, but I should like to point out that our results also suggest that use of preoperative radium gives a better result without selection than does operation alone. For the combined treatment, the gross cure rate was 68.2 per cent, whereas the surgical treatment cure rate gave a lower figure. The patients treated with radiation alone were relatively poor subjects for any treatment; they gave us a very poor cure rate.

It may be preferable to utilize not a pathologic staging, which is post hoc and helps with prognosis but not with treatment, but the three important facets of the disease that can be estimated at fractional diagnostic curettage: (1) size of the uterus, because this tumor grows

locally, (2) advancement of the lesion into the myometrium, and (3) involvement of the cervix by this tumor—both latter qualities suggesting that the parametrium and pelvic lymphatics may be involved. With these criteria one can make a somewhat meaningful clinical classification which can be handled according to one's own prescription for treatment.

In small lesions that are well differentiated there appears to be no difference in the cure rate whether or not one uses preoperative radium. In the lesions of medium advancement, one has a significantly greater cure rate with combined treatment than with operation only. In Stage III tumors, those that are larger, undifferentiated, or involve the cervix, one gets in any case a relatively poor cure rate, which is improved with preoperative radium; these patients require a more radical treatment, such as radical hysterectomy and pelvic node dissection, or extended radiotherapeutic effort.

DR. ERLE HENRIKSEN, Los Angeles, California. In repeatedly emphasizing planned therapy we have overlooked an extremely important factor in the management of this disease. Of equal, if not greater, importance is a planned method of establishing the diagnosis. The use of Hegar-type dilators, or any similar instrument capable of exerting intrauterine pressure, definitely increases the risk of spread. The danger of accelerating cellular spread by the curette must also be borne in mind. I do not imply that the curette should be discarded, for when judiciously used it is invaluable. The very nature of the lymphatic vessels, the blood vessels, and the tissue spaces in relation to the cancer emphasizes the need for gentleness in even the most simple procedure.

There is a definite place for irradiation, especially when the lesion is located in the lower portion of the uterus. The spread pattern at this level is almost identical with that of a cervical carcinoma. As for the so-called vaginal vault recurrences, it was not too many years ago that we sutured the cervix to prevent the spill of cancer cells. I was a bit more scientific in that I packed the canal with gauze, thus making it more difficult for these cells to filter through. Careful examination of the paravaginal tissue clearly demonstrates that these "recurrences" are not the result of spill but are undisputable evidence that the planned therapy was inadequate.

Careful review of the physiopathological prob-

lems inherent in the natural history of this disease produces no evidence in support of so-called radical operation. Even the ultraradical excisions fall far short of the complete removal of all the potential sites. It is well to bear the thought in mind that an incomplete operation may do far more harm than good.

DR. CHARLES E. McLENNAN, Palo Alto, California. Table I shows the result of our planned program at Stanford, which was to remove all endometrial carcinomas surgically without preoperative irradiation. At that time we had a small series of 88 patients showing a survival rate of approximately 90 per cent, irrespective of whether they were treated surgically alone or with preoperative irradiation.

Table II shows these figures brought up to date 3 years later. Again almost 90 per cent are surviving. To be sure, there is a very minor drop of survival rate in the series of patients who had operation alone, but, of the 10 patients lost, 5 died of intercurrent disease, and we might say that at least 93 per cent outlived their carcinomas. There were only 3 deaths due to carcinoma out of those 10; 2 patients were lost during 4 years of follow-up but were well when last seen.

Table I. Endometrial carcinoma, Stanford Hospital, San Francisco, 1940-1951

Therapy	No. treated	Survived 5 years	Survival rate (%)
Operation alone	43	40	93.0
Radiation and operation	23	21	91.5
Radiation alone	22	11	50.0
Total	88	72	81.8

Table II. Endometrial carcinoma, Stanford Hospital, San Francisco, 1940-1954

Therapy	No. treated	Survived 5 years	Survival rate (%)
Operation alone	74	64*	86.5
Radiation and operation	28	25	89.2
Radiation alone	25	14	56.0
Total	127	103	81.0

*Five of the 10 losses due to intercurrent disease in cancer-free patients; thus, 93 per cent outlived the cancer.

I would suggest again that radium probably plays no useful role in the control of this disease and that the ideal clinical experiment has not yet been performed by any of us, that is, the selection of alternate patients for treatment with and without preoperative irradiation.

DR. MONTGOMERY (Closing). Most of these patients were treated during the years when we used intrauterine irradiation freely to control benign uterine bleeding. Radium was inserted into the endometrial cavity at the time of the diagnostic curettage. If the pathologist's report, which was available within 6 to 24 hours, revealed carcinoma, the radium was already in place and its destructive influence on the carcinoma had been instituted immediately after the trauma of the curettage. If the lesion was benign the radium was removed after an exposure of 1,500 to 2,000 mg. hr. in appropriate cases. Follow-up studies on 850 women so treated for benign bleeding revealed subsequent pelvic malignancy in 1.5 per cent of the patients. Some additional malignancies have occurred among these women in recent years, and the incidence of malignancy has risen to 3 or 4 per cent. We no longer apply radium without a positive or a strongly suggestive diagnosis.

However, we continue to be concerned about the possible spread of the lesion as the result of

the trauma of curettage. When cytology smears are Class IV or V and the curettings are grossly suggestive of carcinoma in postmenopausal women we believe that it is to the patient's advantage to apply the radium immediately and confirm the diagnosis either by frozen section or routine sections within 24 hours.

Only one of our patients with carcinoma extending beyond the uterus survived for 5 years. This patient had involvement of one ovary only. Five patients who were thought to have favorable prognoses were found to have pelvic nodes involved. They all died within 1 or 2 years.

Our Department of Radiology and Radiation Therapy has always been responsible for the care of our radium, which has been calibrated at regular intervals.

I am glad that Dr. Henricksen pointed out the dangers of undue manipulation. We believe that this may be an important factor in the spread of the disease.

Dr. McLennan's results are superb. In our hospital we encounter a good many poor-risk patients who have had symptoms for a long time and I wonder whether our cases are comparable. His results indicate clearly that irradiation is not always necessary. However, we believe that if irradiation adds only a few cases of survival, its use is amply justified.

Stage I carcinoma of the uterine cervix

Comparison of results with variations in treatment

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THIS report represents a 16 year experience with International Stage I carcinoma of the uterine cervix treated primarily at the North Carolina Baptist Hospital (NCBH) from 1943 to 1958. One hundred and eighty-four patients comprise this group. All of the patients have been staged and the treatment supervised by one observer (F. R. L.). Selection of method of treatment has been decided by a joint conference of the Gynecology and Radiation Therapy Departments. The patients have come from a stable geographic area which has permitted frequent and prolonged observation. Only one of the 184 patients has been lost to follow-up examination. The rather unique characteristics of this group permit a controlled comparison of results with variations in management.

Radiation therapy has been the basic plan of treatment because of the reported good results with low morbidity. Disappointed by the appreciable incidence of early and late

pelvic recurrence, we supplemented the full course of radiation therapy with elective radical hysterectomy where it was feasible. Later, following Taussig's report¹² on early lymph node metastases, regional pelvic lymphadenectomy was added.

In 1955, Co⁶⁰ replaced radium for intracavitary therapy and after 1956 the gamma rays of a telecobalt unit replaced orthovoltage x-ray for external radiation. At that time primary treatment was changed to intensive radiation with radical operation reserved for proved or suspected persistent carcinoma. Throughout this entire experience, primary radical operation was utilized for a limited number of selected patients.

It is our purpose to describe the experience with these various groups.

Diagnosis

A policy of routine biopsy of all cervixes with a visible lesion and in all patients before hysterectomy was maintained prior to the advent of the Papanicolaou smear as a reliable clinical tool. By this means a number of very early lesions were diagnosed.⁶ After 1953, use of the Papanicolaou smear became standard practice. Patients with positive smears and biopsies showing intraepithelial carcinoma were subjected to wide knife conization for definitive diagnosis. As a result, more early lesions and intraepithelial lesions with minimal invasion, "microcarcinoma," were diagnosed. In 4 pa-

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tients, invasive carcinoma was not diagnosed before hysterectomy and in each case the above-outlined diagnostic procedures were not followed completely.

Material

From Jan. 1, 1943, to Dec. 31, 1958, 387 patients with carcinoma of the cervix received primary treatment at the NCBH. One hundred and eighty-four (47.5 per cent) of these had Stage I lesions. The lesion involved a cervical stump in 13 patients (7.1 per cent). One hundred and seventy-one women had intact uteri. We have subdivided Stage I lesions as follows: Ia, no visible lesion; Ib, lesion 1 cm. or less, and Ic, lesion more than 1 cm.² Substage distribution, histology of the lesions, socioeconomic status, and age distribution of the patients are listed in Table I.

Pretherapy evaluation for all patients consisted of a complete history and physical examination and pelvic examination by members of the Gynecology and Radiation Therapy Departments. When pelvic findings conflicted, those of one observer (F. R. L.) were used in an effort to standardize clinical staging. In all cases the clinical lesion was understaged when exact definition was doubtful. Adjunctive studies in addition to a complete blood count and urinalysis included chest x-ray examination, an excretory pyelogram, barium enema, and determinations of blood urea nitrogen and total serum protein concentrations. Cultures, electrocardiograms, additional blood chemical studies and x-ray examinations, cystoscopic and proctoscopic procedures were performed when indicated. At a joint conference of the Gynecology and Radiation Therapy Departments, therapy for each patient was decided based on the above evaluation.

The patients fall into 6 distinct therapeutic categories: Group I, primary radiation therapy by radium and orthovoltage x-ray; Group II, primary radiation by radium and orthovoltage x-ray with elective radical operation; Group III, primary radiation therapy by Co⁶⁰ applicator and telecobalt

radiation; Group IV, primary radical operation; Group V, miscellaneous therapy; Group VI, carcinoma of the cervical stump.

Group I, primary radiation by radium and orthovoltage x-ray. Thirty-eight patients received radium in a "T" tube or Ernst applicator for 5,000 mg. hr. The intensity of the intracavitary application varied from 50 mg. radium in the "T" tube to 70 or 90 mg. radium in the Ernst applicator. External radiation was given with a 220 kv. Westinghouse constant potential x-ray machine with a Thoreus II filter of half value layer 1.4 mm. Cu with an output of 78 r per minute in air at 50 cm. target-skin distance. External therapy was administered by two anterior 8 by 15 cm. ports separated by a 4 cm. wide lead strip and similar parallel opposing posterior ports. After 1955, two 10 by 10 cm. right and left oblique sacrosciatic ports were added. External radiation was given to skin tolerance which varied from 2,700 to 3,300 r on skin per port. In the majority of patients an initial single radium application was followed by the external therapy in an overall time of 5 to 7 weeks.

Group II, primary radiation by radium and orthovoltage x-ray with elective radical operation. An additional 50 patients received radium and orthovoltage x-ray as described above plus elective radical operation. Hysterectomy and bilateral salpingo-oophorectomy, en bloc resection of regional lymph nodes below the aortic bifurcation, wide parametrial resection including dissection of the ureters from their broad ligament tunnels, and resection of at least the upper third of the vagina and paravaginal tissues were performed. Regional lymph node resection was not performed on 22 patients. The time interval between radiation and operation varied from 1 to 10 months, but averaged 3 to 4 months. Of the 38 nonoperated patients (Group I), we could find reasons to contraindicate operation in only 17. Three patients refused operation. In another 3, associated medical disease made operation inadvisable. Ten patients were 60 years of age or older. Only

Table I. Distribution of lesions and patients (intact uterus)

	Entire series (%)	Group I (%)	Group II			Group III (%)	Group IV (%)
			Entire group (%)	Without lymphade- nectomy (%)	With lymphade- nectomy (%)		
<i>Histology</i>							
Squamous cell carcinoma	93	97	90	90	89	93	91
Adenocarcinoma	5	3	6	5	7	5	9
Undifferentiated carcinoma	2	0	4	5	4	2	0
<i>Substages</i>							
Ia (no visible lesion)	7	5	8	14	4	5	17
Ib (lesion 1 cm. or less)	36	37	24	32	18	23	57
Ic (lesion over 1 cm.)	57	58	68	54	78	72	26
<i>Age distribution (years)</i>							
24-29	3	0	2	5	0	0	13
30-39	28	16	50	59	42	18	30
40-49	30	34	28	27	29	25	35
50-59	25	24	20	9	29	32	22
60-69	11	21	0	0	0	18	0
70-73	3	5	0	0	0	7	0
<i>Socioeconomic status</i>							
Service patients	58	68	68	82	57	50	35
Private patients	42	32	32	18	43	50	65

laparotomy was performed 4 months after radiation in one instance because cancer-bearing aortic nodes were present.

With the exception of age distribution (Table I), Groups I and II are quite comparable. Patients in Group II, with and without regional lymph node resection, are also comparable except for a greater number of Stage Ic lesions in the former (Table I).

Group III, primary radiation therapy with Co⁶⁰ applicator and telecobalt radiation. In 40 patients, a rigid tripartite applicator with a central uterine tandem and 2 adjustable colpostats loaded with europium¹⁵² or Co⁶⁰ was used for intracavitary therapy.^{8, 10} Optimal application was designed to deliver a maximum of 4,000 gamma roentgens to the bladder and rectum, 6,000 to 7,000 gamma roentgens to Tod's Point A, and 7,000 to 12,000 gamma roentgens to the cervix. External radiation was given from a Keleket-Barnes telecobalt machine with an output of 85 r in air per minute at 50 cm. source-skin distance. This supervoltage energy is comparable to the

effect of a 2 to 3 Mev. x-ray beam. Radiation was administered by two 6 by 14 cm. anterior ports with 6 to 9 cm. separation and similar parallel opposing posterior ports. Dosage depended on the desired dose to "Point W." This is a lateral pelvic wall index point situated on the inner margin of the acetabulum and is taken to be 6 cm. from the midline. It is about 1 cm. lateral to Tod's Point B, and dosages to each are essentially the same. The same sequence of local and external therapy was used as described for Group I over 4 to 5 weeks. Radiation dosimetry for both groups is given in Table II. In Group I, bladder and rectum doses were not calculated. Group III is divided into three subgroups differing by about 1,000 roentgens at Point A and Point W. They are labeled III_L, III_M, and III_H in the order of increasing dosage. Doses to the various index points are a summation of intracavitary and external radiation doses without correction for energy differences in the two modalities. Substage distribution is listed in Table I.

Radical hysterectomy and regional lym-

phadenectomy was performed in 6 patients and exenteration in 2 patients for proved or presumptive persistence.

Group IV, primary radical operation. Twenty-three carefully chosen patients were treated by primary radical operation as described for Group II (Table I). Regional lymphadenectomy was omitted in one patient. One or both ovaries were left in selected patients. Seventeen patients in Stage Ia and Ib had minimal or no clinical lesions, 11 of which were confirmed preoperatively by knife conization. Of the 6 patients in Stage Ic, 2 had adenocarcinoma and 3 had well-differentiated squamous cell lesions. The one patient operated upon without lymphadenectomy had an intraepithelial carcinoma on preoperative punch biopsy but invasion was found in the surgical specimen.

Group V, miscellaneous therapy. This group comprises 4 misdiagnosed cases and 16 in which radiation therapy was compromised by various factors. Six of the latter patients had radical operation as part of the definitive therapy.

Group VI, carcinoma of the cervical stump. Treatment of 13 patients with carcinoma of the cervical stump consisted of radiation alone in 5 and primary radical operation in 8. Ages ranged from 30 to 65

years and averaged 51 years. One Stage Ia, 7 Stage Ib, and 5 Stage Ic patients were treated.

Results

Group I. Of 38 patients, 26 (68.5 per cent) are living without recurrence 4 to 14 years after treatment (one at 4 years; 12 from 5 to 7 years; 5 from 8 to 9 years; 8 over 10 years). Eleven patients died of recurrent tumor (5 in the first year after treatment; 2 in the second; 2 in the third; 1 in the fifth; and 1 after 5 years). One patient died of ovarian carcinoma 38 months after treatment for cervical malignancy. No evidence of persistent cervical carcinoma was present.

Significant complications of treatment occurred in 3 patients (7.9 per cent). These consisted of radiation sickness severe enough to require hospitalization, necrosis of the vaginal wall, and a pulmonary embolism during treatment.

Group II. Twenty-two patients were treated without regional lymphadenectomy. Nineteen (86.4 per cent) are living without recurrence 9 to 15 years after treatment. One operative death occurred from peritonitis. One patient died of recurrent cancer at 43 months and one died of a stroke 11 years after treatment. Postmortem exami-

Table II. Summary of radiation techniques and dosimetry

Radiation therapy—modalities				
Groups I and II	Intracavitary External	Radium in "T" tube or Ernst applicator Orthovoltage x-ray, 220 kv.		
Group III	Intracavitary External	Europium ¹⁵² or cobalt ⁶⁰ in tripartite applicator telecobalt radiation		
Radiation therapy—dosimetry (intracavitary plus external)				
	<i>Cervix</i>	<i>Point A</i>	<i>Point W</i>	<i>Bladder-rectum</i>
Groups I and II	11,600 r* (9,800-12,600)	7,000 r* (6,950-7,200)	3,500 r* (3,400-3,600)	—
Group III _L	9,900 r (8,200-11,600)	8,600 r (7,500-10,100)	4,000 r (3,000-4,400)	4,800 r (4,500-5,300)
Group III _M	10,600 r (8,900-12,400)	9,400 r (8,700-10,700)	4,900 r (4,700-5,100)	5,300 r (3,900-6,800)
Group III _H	12,300 r (10,700-13,900)	10,700 r (9,300-13,100)	5,700 r (5,400-6,900)	6,800 r (4,700-9,100)

*Total of intracavitary gamma roentgens and external x-ray.

nation showed no evidence of cancer. This is the only death in the entire series corrected in the results and for these 22 patients gives a 9+ year survival of 90 per cent. Eight severe complications of treatment (36 per cent) occurred, only 4 of which are directly attributable to operation (1 operative death, 1 pulmonary embolism, 1 ureteral stricture, and 1 rectovesical fistula). Three patients had persistent radiation proctitis and one required hospitalization for nausea and vomiting during radiation therapy. Only one patient had persistent cancer which was localized to the cervix. This has not recurred.

Of 28 patients treated with regional lymphadenectomy, 23 are living without recurrence. Eighteen patients are living over 5 years after treatment, and 5 are living between 4 and 5 years (82.3 per cent). Persistent cancer and death occurred in 4 patients, 7, 10, 18 and 27 months after treatment. One woman is living with recurrence 8 years after initial therapy. Seven severe complications of treatment occurred in the group (25 per cent). With the exception of one patient with radiation proctitis, all the complications were from operation. They include 1 postoperative pelvic abscess, 1 pulmonary embolism, 2 ureteral strictures, and 2 vesicovaginal fistulas. Persistent carcinoma was present in only 3 patients. This involved the regional lymph nodes alone in 2 patients and the cervix and lymph nodes of the other patient.

Over-all, these 50 patients have a corrected survival of 86 per cent. Thirty per cent had severe complications of therapy, two thirds of which are attributable to operation. Six per cent developed postoperative fistulas. One operative death occurred.

Group III. Forty patients in this recent group were treated with Co⁶⁰ and telecobalt radiation. The distribution of patients into dosage groups seems arbitrary until the results in each group are analyzed. When complications of radiation therapy alone and those of supplemental operation are considered, the significance of the subgroups is obvious (Table III). In subgroups III_L

and III_M the incidence of significant radiation complications is increased to 25 per cent, but in subgroup III_H, 70 per cent of patients had significant complications. These complications will be the subject of a future report.

Each subgroup is so small that survival has been considered only for the entire group. Thirty patients are living without recurrence 15 to 53 months (median 28 months) after treatment. Three of these had additional radical operations for presumptive persistent cancer which was present in only one patient. Five women died of persistent cancer 4, 10, 11, 12, and 25 months after treatment, and 2 women without recurrence died from treatment alone. Three patients are living with extensive recurrence 33, 37, and 49 months after treatment.

Eight of these 40 patients had supplemental radical operation. Exenteration was performed on 2 patients with definite recurrence. Both died within 2 weeks of operation. Radical hysterectomy and pelvic lymphadenectomy were performed on 6 patients. Two patients with proved persistent cancer 6 and 16 months after treatment had no operative complications. Of 4 patients with negative surgical pathology, 2 developed vesicovaginal fistulas and 2 died 3 months postoperatively of progressive pelvic necrosis. Thus, 2 of 3 patients in subgroup III_M treated with intensive radiation and radical operation developed focal pelvic necrosis (fistulas), and 2 of 3 similarly treated patients in subgroup III_H developed total pelvic visceral necrosis.

Group IV. Twenty-two patients were treated with primary radical operation as described and one with radical hysterectomy alone. Two patients with lymph node metastases had postoperative x-ray therapy.

Surgical pathology. No tumor was found in 8 specimens; 7 after conization and 1 after punch biopsy. Residual intraepithelial carcinoma was present in 4 specimens; 3 after conization and 1 after punch biopsy. In 6 specimens invasive tumor was confined to the cervix and in 5 others invasive carcinoma involved both the cervix and regional

Table III. Complications of intensive radiation therapy

	No. patients	Complications (%)
<i>Group III_L (8 patients)</i>		25
Septicemia during treatment	1	
Radiation sickness	1	
<i>Group III_M (12 patients)</i>		25
Excessive pelvic fibrosis	2	
Vaginal fibrosis	1	
<i>Group III_H (20 patients)</i>		70
Subcutaneous lignification	11	
Excessive pelvic fibrosis	3	
Vaginal fibrosis	2	
Ureteral stricture	1	
Focal stricture of ileum	1	
Severe chronic cystitis with bleeding	2	
Severe chronic proctitis with bleeding	2	

Table IV. Results—carcinoma of cervical stump

	No. patients	Survival (%)
<i>Radiation therapy</i>	5	
Living without recurrence (7+ years)	3	60
<i>Primary radical operation</i>	8	
Living without recurrence (16 to 84 months)	6	75
Lymph node metastases	2	
Living without recurrence after node metastases (50 and 84 months)	2	100
<i>Over-all survival without recurrence (16 months to 11 years—median 54 months)</i>	9	69

Table V. Summary of results on surgically treated patients

	Groups I and II				Group III		Group IV (23 patients) (%)
	Radiation only (38 patients) (%)	Plus elective radical hysterectomy (22 patients) (%)	Plus elective radical hysterectomy and lymphadenectomy (28 patients) (%)	Plus radical operation (50 patients) (%)	Radiation only (34 patients) (%)	Plus indicated radical hysterectomy and lymphadenectomy (6 patients) (%)	
Complications	8	36	25	30	56	83	9
Radiation induced	8	18	4	10	56	17	-
Operation induced	-	18	21	20	-	66	9
Fistulas	0	5	7	6	0	33	5
Operative mortality	-	5	0	2	-	33	4
Positive operative pathology	-	5	11*	8	-	33	22*
Survival without recurrence	68.5	86	82	84	79	50	96
Corrected	-	90†	-	86	-	-	-

*Incidence of lymph node metastases.

†Died of stroke 11 years after therapy; no tumor at autopsy.

lymph nodes. Of the 5 specimens with lymph node involvement 2 were Stage Ib and 3 were Stage Ic.

Complications of treatment. Transient small lymphoceles were noted in 2 patients. One ureterovaginal fistula occurred and one patient died on the operating table of uncontrolled hemorrhage.

Survival. One operative death occurred in a patient with lymph node metastases. The remaining 22 patients are living without recurrence from 13 months to 10 years (median 37 months) after treatment. Nine patients are surviving from 5 to 10 years and 4 patients with lymph node metastases are living 36, 38, 49, and 72 months after therapy.

Group V.

Misdiagnosed. Four patients had vaginal or abdominal hysterectomy for undiagnosed invasive squamous cell carcinoma. All lesions fell in Stage Ib. One patient received external radiation therapy postoperatively. These 4 patients are surviving without recurrence 9, 10, 13, and 14 years after therapy.

Modified therapy. In 10 patients with Stage Ib lesions and 6 with Ic lesions, therapy had to be modified because of associated medical disease, a second malignancy, or intolerance to radiation therapy. Twelve received local radiation only and 4 received external radiation only. In 6 patients therapy was complemented with elective radical operation.

Of the 10 patients receiving only radiation, 3 are living without recurrence 5, 6, and 13 years; 1 is living with recurrence; 5 died of the disease; and 1 schizophrenic patient was lost to follow-up. The surviving women each received local radium alone for Stage Ib lesions.

Of 6 patients operated upon, 2 had Stage Ib and 4 had Stage Ic lesions. Operation complemented local radium in 5 and external radiation in 1 patient. Only 1 had a focus of residual tumor around one tube. All 6 patients are surviving without recurrence 4, 6, 10, 11, 12, and 16 years.

Over-all, 65 per cent of these patients are surviving without recurrence. Thirty per

cent of those with modified radiation alone and 100 per cent with additional radical operation survive.

Group VI. Of 5 patients treated with radiation only 3 are surviving without recurrence 7, 10, and 11 years. Two patients had recurrence 11 and 19 months after treatment and died.

Eight patients were treated with radical trachelectomy and regional lymphadenectomy. Tumor was not identified in 2 specimens; one after preoperative conization, and one after preoperative external radiation. Invasive cancer was confined to the cervical stump in 4 specimens and involved the lymph nodes and cervix in 2 specimens. Six patients are surviving without recurrence 16 months to 7 years. One patient with negative surgical pathology findings developed recurrence 52 months later and died. One other patient died without recurrence in an automobile accident 5 months after treatment.

Nine of the 13 patients in this group (69 per cent) are surviving from 16 months to 11 years (median 54 months). Two patients with lymph node metastases are living and well after 46 and 84 months (Table IV).

Summary of results. A summary of results in operated patients is presented in Table V. Patients with combined operation and high dosage radiation are shown to emphasize the frequency of complications. Results for all patients with intact uteri are given in Table VI by therapy, substage, and carcinoma cell-type.

Comment

It is established that early carcinoma of the uterine cervix can be treated effectively by radiation, radical operation, or combinations of these methods. Generally, reports deal with one method of therapy and with lesions of various clinical stages. It is difficult to compare experience with various therapeutic modalities in different series because of inherent individual differences and often lack of specific details. In this report the patients are quite comparable in all respects except for method of treatment and

age distribution. We believe that the various groups represent satisfactory controls for each other in terms of complications and current results. Moreover, Groups I and II are entirely comparable since all of the patients have been observed for more than 4 years and since 9 of the 10 nonoperated women over 60 years of age are living without recurrence.

Problem of early metastases with Stage I lesions. The rationale of pelvic lymphadenectomy in the treatment of cervical carcinoma still is questioned¹¹ although survival after resection of cancer-bearing lymph nodes is well documented. Comparison of survival in the small number of Group II patients with and without regional lymphadenectomy again raises this problem. The well-established inaccuracies of clinical staging are confirmed by the 22 per cent incidence of lymph node metastases in the patients operated primarily. There was a 50 per cent reduction in cancer-bearing lymph nodes after radiation therapy (Group II). One would expect more metastases to occur in the advanced Stage I lesions. Twenty-nine specimens with regional lymph nodes obtained prior to any radiation therapy were available. Seven specimens contained lymph node metastases distributed as follows: 1 of 5 specimens in Stage Ia; 3 of 17 specimens in Stage Ib; and 3 of 7 specimens in Stage Ic. The metastatic potential of even the earliest lesions was demonstrated again in a patient with microcarcinoma diagnosed by knife conization. Two days after conization radical operation was performed. Although no residual tumor was found in the resected specimen, circulating cancer cells were recovered from uterine vein blood drawn at the time of radical operation.

Since even the earliest of invasive cervical lesions are associated with a definite but as yet undefined number of metastases, there can be no compromise with accepted methods of treatment. We cannot agree with the recent report³ suggesting that the one cm. lesion is a critical size below which the number of metastases are so few as to justify simple hysterectomy as complete defi-

nitive therapy. However, it appears that a better prognosis is probable with the earlier lesions² (Table VI).

Of 11 patients with lymph node metastases, 6 are surviving without recurrent disease 36, 38, 39, 46, 72, and 84 months. Pelvic lymphadenectomy made possible a 54 per cent survival in these 11 patients. In spite of conflicting reports in the literature,^{5, 7, 11} a definite number of patients will be saved by the procedure. Since pelvic lymphadenectomy in conjunction with radical hysterectomy adds little to operative time and morbidity, it should remain an essential part of the surgical therapy of cervical carcinoma.

A 68.5 per cent survival was obtained in Group I with a 7.9 per cent incidence of severe morbidity. These patients received radiation dosage within the optimum levels for cervical carcinoma as described by Nolan⁹ and Garcia.⁴ The addition of elective radical surgical resection improved survival 18 per cent. Although morbidity increased to 30 per cent, most of the complications were transient and certainly are justified by the results. Can the increased survival be explained? Only 4 patients had proved residual tumor and 3 of these with lymph node metastases died. A total of 68 lymph node resections were performed. Without the use of special techniques the number of lymph nodes recovered by the pathologists per side varied from zero to 19. An average of 6 nodes were recovered per side and none were recovered from 9 sides. It is logical to assume that residual tumor was present in more cases but was not found. Although improved techniques may have recovered more lymph nodes, we believe that the residual cancer cells probably were in lymphatic channels proximal to the lymph nodes. Viable tumor cells may be trapped by radiation therapy and further growth stopped or delayed. Removal of those cells destined to continued growth would explain the improved survival.

Intensive radiation therapy. Intensive radiation was accomplished in 32 patients at the expense of a 53 per cent incidence

Table VI. Comparison of results (intact uterus)

	Survival without recurrence (%)	Complications (%)
Therapy		
<i>Groups I and II. Radium and orthovoltage x-ray</i>		
Radiation only (38 patients)	68.5	8.0
Radiation plus radical operation (50 patients)	86.0*	30.0
<i>Group III. Cobalt⁶⁰ and telecobalt</i>		
III _L (8 patients)	62.0	25.0
III _M (12 patients)	86.0	25.0
III _H (20 patients)	75.0	70.0
Primary radical operation (23 patients)	96.0	9.0
Miscellaneous therapy (20 patients)	65.0	-
Total (171 patients)	78.0	
Substage		
Ia (12 patients)	92.0	
Ib (62 patients)	87.0	
Ic (97 patients)	71.0	
Histology		
Squamous cell carcinoma (158 patients)	79.0	
Adenocarcinoma (9 patients)	67.0	
Undifferentiated carcinoma	50.0	

*Corrected.

of significant and predominantly irreversible complications. This morbidity has been offset by increased survival to date but it would appear that 5-year survival will approximate that obtained with lower radiation levels. The rationale of intensive radiation therapy centers around the concept that a greater number of primary lesions and lymph node metastases can be eliminated if higher dosage is administered, at the same time staying within limits of a reasonable morbidity rate. Supervoltage radiation permits a test of this concept. Although our experience in this area is limited in time and number of patients treated, it is apparent that such a therapeutic program is not feasible. Optimum radiation levels are those which effect the greatest number of "cures" with the least morbidity. Survival with therapy sequelae that significantly impair the "whole patient" is unacceptable. Moreover, a probable ultimate lack of improved survival in this series (1) is consistent with the findings of Brown and his co-workers¹ indicating that intensive radiation will not eliminate radioresistant lesions, and (2) suggests that the "supralethal effect" concept of radiation may be a contributory factor.

Initial maximum tolerable radiation therapy precludes further radiation for persistent or recurrent local lesions. In addition, the amount of pelvic fibrosis is great and often progressive so that clinical evaluation of the pelvis is totally unsatisfactory. Radical operation is the only remaining method of treatment for persistent tumor. However, in our experience the subsequent morbidity and mortality are prohibitive. The combined devascularization of vital structures from intensive radiation and radical operation is too great for the average patient. Under these circumstances intensive radiation becomes an all-or-none approach to therapy. As more and more supervoltage radiation units become available, there will be a natural tendency for radiotherapists to increase radiation dosage in an effort to improve survival. No longer will they be limited by skin tolerance dosage. The average gynecologist either refers his patients completely to the radiotherapist or else participates in their therapy only to a limited extent. In either case he usually is not cognizant of the critical significance of the radiation dosage administered. Therefore, only as radiation levels creep insidiously upward will the gynecologist recognize the pit-

fall of these circumstances. We hope that our experience will avert this course of events. It must be emphasized that this experience is not an indictment against super-voltage therapy per se but only against the excessive radiation possible with it.

Radical surgical therapy. Our experience with radical operation in the treatment of cervical carcinoma has been quite favorable. However, the exceptionally good results obtained with primary radical operation cannot be accepted without qualifications. The majority of patients were young women with lesions we consider best treated by primary resection. The operative pathology and survival to date confirm these decisions. Unusual success with these patients so far permits a 96 per cent survival. Assuming that all patients with node metastases should die of recurrence, survival would fall to 78 per cent.

We believe primary radical hysterectomy and pelvic lymphadenectomy to be the treatment of choice for the young woman with microcarcinoma, especially if continued ovarian function is desired. Radical trachelectomy with pelvic lymphadenectomy is our preferred treatment for carcinoma of the cervical stump. Following a full course of moderate dosage radiation therapy, these procedures can be performed safely and without unusual difficulty or prohibitive morbidity. On the other hand, after intensive radiation in the ranges previously outlined, unduly high postoperative morbidity and mortality contraindicates radical operation. To be successful, radical pelvic operation must be performed on carefully selected patients by trained and experienced surgeons in an institution prepared for any exigency that may arise.

Conclusions

1. Optimal dosage levels of pelvic radiation as described by Nolan and Garcia may be supplemented by radical hysterectomy and pelvic lymphadenectomy for the treatment of Stage I cervical carcinoma without a prohibitive increase in complications. This combination yielded an increase in survival rate from 68.5 per cent with radiation therapy alone to 86 per cent.

2. Intensive pelvic radiation probably does not improve survival in patients with cervical carcinoma. Moreover, the incidence of radiation complications is unduly high. The high incidence of pelvic necrosis following subsequent radical operation is prohibitive.

3. Primary radical operation in selected patients yields excellent results.

4. Earlier diagnosis within Stage I improves survival with cancer of the cervix, but even the earliest of invasive lesions must be treated as though metastases had already occurred.

5. Therapy must be individualized for every woman with cervical carcinoma to obtain maximal survival with a minimum of complications. Treatment must be flexible enough to meet unforeseen problems. Therapy must be planned so that avenues of treatment for recurrent disease are not closed.

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REFERENCES

1. Brown, W. E., Meschan, I., Kerekes, E., and Sadler, J. M.: *AM. J. OBST. & GYNEC.* 62: 871, 1951.
2. Corscaden, J. A.: *AM. J. OBST. & GYNEC.* 59: 272, 1950.
3. Friedell, G. H., and Graham, J. B.: *Surg. Gynec. & Obst.* 108: 513, 1959.
4. Garcia, M.: *Am. J. Roentgenol.* 73: 35, 1955.
5. Hollenbeck, Z. J. R.: *AM. J. OBST. & GYNEC.* 79: 944, 1960.
6. Lock, F. R., and Caldwell, J. B.: *AM. J. OBST. & GYNEC.* 57: 1133, 1949.
7. Meigs, J. V.: *Surgical Treatment of Cancer of the Cervix*, New York, 1954, Grune & Stratton, Inc., p. 192.

8. Meschan, I., Oddie, T. H., and Regnier, G.: *Radiology* 64: 546, 1955.
9. Nolan, J. F., Vidal, J. A., and Anson, J. H.: *AM. J. OBST. & GYNEC.* 72: 789, 1956.
10. Oddie, T. H., and Meschan, I.: *Radiology* 64: 560, 1955.
11. Rauscher, H., and Spurny, J.: *Obst. & Gynec. Surv.* 15: 280, 1960. (*Geburtsh. u. Frauenh.* 19: 651, 1959.)
12. Taussig, F. J.: *AM. J. OBST. & GYNEC.* 45: 733, 1943.

Discussion

DR. HOWARD C. TAYLOR, JR., New York, New York. You have heard all that 15 minutes will permit of a meticulous analysis of a series of 184 patients with Stage I carcinoma of the cervix. The series is important for many reasons, especially because it has been consistently supervised by one observer and further because only one patient of the series has been lost to follow-up.

My discussion will be concerned with one—to me—disturbing implication, namely, that radical hysterectomy and lymph node dissection added to optimal radiation will increase the cure rate. In the conclusion it is stated “this combination yielded an increase in survival rate from 68.5 per cent with radiation therapy alone to 86 per cent.” Since Dr. Lock’s reported experience will have a wide influence, I wish to raise the question of whether this apparent improvement may not be wholly due to selection of cases.

A clinical experiment, perhaps familiar to some of you, was conducted by Dr. Gray Twombly and myself a number of years ago at the Memorial Hospital to examine this question. The 5 year results reported in 1954 dissect the problem so well that I would like to present the figures once more (Table I).

There were 87 Stage I and Stage II cases in the series. These, as they were admitted, were assigned alternately to a radiation series and to an operation with x-ray series. With such a plan there were inevitably some patients, falling by chance in the surgical series, who, for reasons of age, obesity, or complicating illness, could not properly be treated surgically. These, although actually managed radiotherapeutically, made up

a special group. They constituted the usually concealed handicap for which a surgical series is customarily spared statistical accountability.

Table I shows that in the radiation series the cure rate was 71 per cent, and, for the cases actually treated by operation, 79 per cent. However, there were 14 cases assigned to but unsuitable for operation, which were referred to radiation therapy, and among them the cure rate was 16.7 per cent. Note that the group unsuitable for operation also had a cure rate far below that for the general, unselected series of radiation-treated cases. It may be that it is simply the constant assignment of this group, with a poor prognosis by any method of therapy, to the radiation series that so often makes it possible for surgical results to shine by comparison.

The experience with the treatment of Stage I cases at the Columbia-Presbyterian Medical Center may be explained in part on the basis of such selection (Table II).

From 1929 to 1943, treatment exclusively by radiation yielded cure rates which rose from 43 to 76 per cent, apparently as a result of improved methods of radiation therapy.

In the periods 1944 to 1951 and 1952 to 1954, the results from radiation declined, perhaps because many of the most favorable primary cases were being selected for operation. The surgical results from 1944 to 1951 showed an 88.3 per cent cure rate, probably because in this period criteria for selection for operation were very strict. From 1952 to 1954, the results for operation were not quite so good, perhaps because the indications for surgical procedures had been expanded.

It seems to me improbable that the decision between radiation alone and operation plus radiation in Stage I cases can be made on statistical grounds in the foreseeable future. The best available figures for the two methods give results that are nearly identical and the presence of various factors affecting the samples being compared require that quite large differences

Table I. Comparative results

Total cases	87	
Radiation series	44	
Cure rate		71 %
Surgical series	43	
Cure rate for 29 surgical cases		79 %
Cure rate for 14 “unsuitable cases”		16.7 %
Cure rate for “surgical series”		60 %

Table II. Five-year results in Stage I cancer of the cervix in the Presbyterian and Francis Delafield Hospitals

Type of treatment	Total cases	5 year survival	
		No.	%
<i>Radium and x-ray</i>			
1929-1933	31	13	43.0
1934-1938	45	29	64.0
1939-1943	51	39	76.0
1944-1951	66	37	56.0
1952-1954	23	11	47.8
<i>Radium, x-ray, and lymph node dissection</i>			
1952-1954	17	15	88.2
<i>Radical hysterectomy and lymph node dissection</i>			
1944-1951	43	38	88.3
1952-1954	27	19	70.3
<i>Miscellaneous operations</i>			
1944-1954	12	8	66.6
Total cases	315	209	66.3

be demonstrable. The individual operator will probably continue to decide on the basis of personal preferences and on a comparison of complications and later disabilities and will hope for the appearance of some new diagnostic or therapeutic principle that will resolve this deadlock of opinions.

DR. A. N. ARNESON, St. Louis, Missouri. Any assessment of results in cancer necessitates extended observation of patients after treatment, and, if different methods are to be compared, the assurance of dealing with uniform clinical material. The magnitude of that problem is made apparent by inability directly to compare radiation and operation in the treatment of "operable" cases of cervical cancer. It is increasingly possible, however, to use early results for testing a method within shorter periods of observation. The necessary data are developed in life tables showing accumulative survival per cent. This has the effect of considering a group of patients as having been treated on the same day, despite individual differences in period of follow-up. Survival rates for each year of observation after treatment are determined for the numbers of patients then at risk, but the accumulative value is that percentage of the rate for the immediately preceding year. By that means

the weight of early results falls upon all subsequent time intervals and predicts the trend of current therapy.

Any changes predicted by that assessment must be attributed to differences in the effect of treatment or differences in comparability of clinical material. Solution of that problem is aided by the fact that accumulative tables deal with the rate of cancer deaths for each unit of time patients are at risk. Those with an unfavorable prognosis generally die more promptly. Thus, an unusually high or low rate of cancer deaths in the period immediately following treatment indicates a disproportionate incidence of patients with prognosis at variance with others classed in the same stage of advance.

Dr. Williams and I applied the accumulative method to a group of private patients treated by irradiation, and, on the basis of this work, two points may be mentioned in relation to Dr. Lock's presentation. In the first place, we were faced with the frustration that the more recently treated patients classed in Stage II showed a lower relative result at 5 years' follow-up than did patients of the same stage irradiated in prior years. Curves were drawn to show the rate of cancer deaths for each of the two groups. These were found to run parallel after the first year of observation, but in the initial 12 months after treatment the curve for the more recently treated patients followed that for Stage III. That was interpreted as representing a disproportionately high incidence of patients with poor prognosis which significantly affected relative results because the total number of patients was small.

The second point relates to the fact that Stage I cases acquired maximum cancer deaths within shorter periods of follow-up than did Stage II and III cases. That observation may be due to coincidence and may lack real statistical significance. It is, however, reasonable to believe that Stage I cases include tumors with a range in growth potentially wider than that present in more advanced forms. The more virulent lesions may weed out their hosts before forming large and bulky pelvic tumors. Stage I cancers have a disproportionately high incidence of cancer deaths due to distant spread, and experience with pelvic exenteration has shown that a significant number of large pelvic cancers are without lymph node involvement. This is only one example of the differences in tumor behavior that make hazardous any attempt to

classify patients into groups of comparable prognosis.

I believe Dr. Lock and his associates will find accumulative tables useful in their assessment of different methods of treatment. By that means they can weigh the effect of new procedures upon results obtained by the same individuals in the same clinic in prior years. They can also use those tables to detect changes in type of clinical material, and perhaps to search for errors that may be due to unsuspected selectivity. Experiments of the order here in question belong in study groups of well-organized departments such as Dr. Lock's. His experience with higher energy radiations parallels that of others. The potent irradiators available today can lead to diminishing returns. As gynecologists we can harm our patients if we fail to integrate radium

treatment with the program of external irradiation or if inadvisedly we add the trauma of radical operation to previously damaged tissues.

DR. LOCK (Closing). I would like to answer Dr. Taylor's question about the selection of patients. We reported 38 patients treated with standard radiation alone. Actually, most of them were treated prior to the initiation of the surgical program. In 17, we could find reasons or contraindications to operation, none of them related to the type of carcinoma: 3 refused operation, 3 had associated medical disease, and 10 were 60 years of age or over. Fortunately, from the point of view of this report, 9 of the 10 who were over 60 years of age are surviving.

I am anxious to apply the statistical method Dr. Arneson described to our material.

Value of urologic study in the management of carcinoma of the cervix

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SINCE 1929 one of us (H. S. E.) has been interested in the urinary tract complications resulting from various types of gynecologic disease and from the methods of treatment of some of these disease entities. This interest was stimulated by 2 patients: one with a right ureteroperitoneal fistula and urinary ascites resulting from a surgical injury to the right ureter during hysterectomy for fibroids, the other with a vesicovaginal fistula, enormous hydronephroses, terminal chronic pyelonephritis, and urinary ascites resulting from spontaneous perforation of the dilated left ureter, all of which followed irradiation therapy for carcinoma of the cervix. Reports of both of these cases were published in collaboration with Hunner,^{1, 2} and since that time a number of papers dealing with various aspects of such urologic complications have been presented and/or published either alone or with other members of our staff.

The first of these reports resulting from a systematic study of the subject was pre-

sented before the American Gynecological Society in 1939 under the title "The Effect of Carcinoma of the Cervix Uteri and Its Treatment Upon the Urinary Tract."³ The patients whose cases were studied for that report had been treated by a very high intensity radon treatment to the cervical lesions, and the incidence of urologic complications was high, 20 per cent of serious bladder lesions such as hemorrhagic ulcers or fistulas, and 15 per cent of clinically significant ureteral strictures with resulting hydronephrosis or hydronephrosis. We have always felt that one of the most significant observations derived from that study was the fact that the presence of hydronephrosis found in patients before the institution of treatment constituted an extremely grave prognostic sign.

Soon after the completion of that study our methods of irradiation therapy were changed radically and placed under the direction of C. Bernard Brack. The standard technique for radium therapy then became the application of two 25 mg. tubes of radium in tandem intracervically and 50 mg. in a contracervical plaque. Such applications were administered for 24 hours and repeated after an interval of 2 weeks, giving a total radium dosage of 4,800 mg. hr. The deep x-ray therapy has varied from time to time. Most cases were treated with the 400 kv. x-ray machine. The usual technique was to employ 15 by 15 cm. fields, two anteriorly

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and two posteriorly, separated by 3 to 4 cm. in the midline at 400 kv., 5 ma, 70 target-skin distance, with filtration of 1 mm. copper and 1 mm. aluminum, giving half value layer of 3 mm. copper. The fields were sometimes reduced to 15 by 10 cm. or even 10 by 10 cm. in an occasional patient. Daily doses of 250 r were given to the anterior and posterior ports alternately to a total of 2,500 r. The tumor dose, when calculated, varied between 2,035 and 4,000 r. The treatment time varied from 3 to 7 weeks.

During 1949, many patients were given an additional 2,000 r skin dose to the cervix in 4 or 5 divided doses through a 3 cm. vaginal cone at 250 kv. This technique was discontinued in 1950.

In 1953 the external x-ray therapy was given with a 250 kv. x-ray machine in many of the cases. The factors were 250 kv., 50 target-skin distance, 15 ma., with filtration of from 0.5 mm. copper and 1.0 mm. aluminum to 0.66 mm. Sn, 0.25 mm. copper plus 1.0 mm. aluminum, giving a half value layer varying from 1.6 to 3 mm. copper. A calculated tumor dose of 2,500 r to 2,700 r was delivered with this technique.

The combination of radium and deep x-ray therapy described above was calculated to deliver approximately 20,000 r to the cervical canal, 8,000 r to Point A, and just less than 4,000 r to Point B. More recently an attempt has been made to increase the dose at Point B by increasing the external x-ray therapy.

As a result of the 1939 study, we have made an effort since that time to have all patients with carcinoma of the cervix, except those suffering from hopelessly advanced disease, subjected to urologic studies before the institution of treatment and at varying intervals following treatment. These studies include excretory urography and cystoscopic observation of the bladder. For various reasons, we have never been successful in having all patients so studied, but over the years we have accumulated sufficient material to form the basis of several other reports.

In 1949 a second report compiled by 2 of the present authors, Everett and Brack, was presented before the American Gynecological Society.⁴ The most important conclusion derived from that study was that with the lower intensity method of radium administration the incidence of serious urologic complications in those patients who had survived 5 years or more was reduced to an almost negligible minimum, but that an increase in the radium dosage from 4,800 to 6,000 mg. hr. by increasing the amount of radium from 100 to 125 mg. administered with exactly the same time factors led to a high incidence of serious complications. This observation was confirmed by a comparison with other reports gathered from the literature.

For instance, Morton and Kerner's⁵ technique consisted of an initial application of 150 mg. of radium in the form of three 50 mg. sources within the cervix for 20 hours or a total of 3,000 mg. hr. Two weeks later 150 mg. was applied against the cervix for 10 hours or 1,500 mg. hr. Thus, the total radium dosage was only 4,500 mg. hr., but administered in 30 hours. Their incidence of complications was relatively high. On the contrary, Diehl and Hundley,⁶ who administered 6,000 mg. hr. using 100 mg. of radium for 30 hours in two applications 2 weeks apart, reported no demonstrable complications. Similarly, Kimbrough and Muckle,⁷ using 60 mg. of radium for 100 hours, at a single application encountered a negligible amount of postirradiation reaction.

In 1956 we reported the results of such studies on 402 patients treated by irradiation therapy during the years 1943 to 1948, inclusive.⁸ Sufficient time had elapsed for a completion of the 5 year follow-up in all of these patients, and the 5 year survival rate was 34.6 per cent. Of the 402 patients 150 had been subjected to pretreatment urologic study. Of these, in 99 the pretreatment pyelograms had been normal and in this group there was a 5 year survival rate of 49.5 per cent as compared with 25.5 per cent in the 51 patients who had shown pretreatment

Table I. Absolute 5 year cure rate (1949-1953)

Year	Patients treated	Patients living and well		Including Stage 0	Complications (%)
		No.	%		
1949	71	31	43.6	50.0	21.1
1950	59	30	52.0	56.9	10.2
1951	60	26	41.9	56.4	20.0
1952	42	12	26.7	59.2	11.9
1953	63	29	44.0	58.2	19.0
Total	295	128	43.4	56.7	16.9

Table II. Complications in 295 patients (1949-1953)

Complication	No.	%
Hydronephrosis and hydroureter	11	3.7
Ureteral stricture	4	1.4
Vesicovaginal fistula	8	2.7
Rectovaginal or enterovaginal fistula	7	2.4
Vesicovaginal and rectovaginal fistulas	7	2.4
Ureterovaginal fistula	2	0.6
Bladder ulcer	1	0.3
Massive necrosis	5	1.7
Skin reaction	5	1.7
Total	50	16.9
Total urologic	33	11.2
Complications in living patients		10.7

hydroureteronephrosis. The incidence of all complications in the patients who had survived for 5 years or more was 13 per cent.

The present report is based on the study of 295 patients with all stages of carcinoma of the cervix treated by irradiation during the years 1949 to 1953, inclusive. Of these, 43.4 per cent have survived 5 years or more. If we include the patients with Stage 0

carcinoma treated surgically, the 5 year survival rate for the period was 56.7 per cent. The incidence of complications in this group of 295 patients including those who did not survive 5 years was 16.9 per cent (Table I). The incidence of such complications in those patients who had survived 5 years or longer was 10.7 per cent, showing a definite reduction as compared with the 1943 to 1948 period. The type and incidence of complications encountered for the entire group are shown in Table II. If we eliminate from Table II the complications which were not urologic, there remain 33 urologic complications for the entire group, an incidence of 11.2 per cent.

Prognostic value

One of the most significant values of such urologic study continues to be the prognostic aid obtained from the pretreatment pyelograms. Of the 295 patients treated, pretreatment pyelograms were obtained in 215. In 148 of these patients the pyelograms were normal, and the 5 year survival rate in this group was 70.3 per cent as compared with 22.4 per cent in the 67 patients whose pretreatment pyelograms showed hydronephrosis (Table III). We were rather surprised to find that the carcinoma in 31 of the patients showing pretreatment hydronephrosis was in Stages I or II. In our 1939 study such findings were confined to patients with Stage III carcinoma and served to aid in the prognosis for those patients with this more advanced stage of disease only. Combining these figures with those from the 1956 report we have an 11 year period, 1943 to

Table III. Survival (1949-1953)

Stage	Original pyelograms normal	Living and well 5 years		Original pyelograms hydronephrosis	Living and well 5 years	
		No.	%		No.	%
I	50	45	90.0	7	4	57.0
II	65	45	67.5	24	7	29.1
III	29	14	48.3	28	4	14.0
IV	4	0	0	8	0	0
Total	148	104	70.3	67	15	22.4

Table IV. Comparison of survival rate (1943-1948 and 1949-1953)

Years	Original pyelograms normal	Living and well 5 years		Original pyelograms hydronephrosis	Living and well 5 years	
		No.	%		No.	%
1943-48	99	49	49.5	51	13	25.5
1949-53	148	104	70.3	67	15	22.4
Total	247	153	62.0	118	28	23.7

1953, inclusive. Table IV shows this relationship for the total period.

Of 99 patients in whom the pretreatment pyelograms were normal, the posttreatment pyelograms remained normal in 77 patients, and, of these, 61 (79 per cent) remained well for more than 5 years. Of the 22 pa-

Table V. Five-year survival (1949-1953) correlated with pre- and posttreatment pyelograms

				<i>Living and well 5 years</i>	
<i>Pretreatment</i>		<i>Posttreatment</i>		<i>No.</i>	<i>%</i>
Normal	99	Normal	77	61	79.0
Normal	99	Hydronephro-			
Hydronephro-		sis	22	6	27.3
sis	36	Improved	21	9	42.9
Hydronephro-					
sis	36	Unchanged	15	2	13.3

tients who developed evidence of hydronephrosis following treatment only 6 (27.3 per cent) survived for more than 5 years. Thus, the development of hydronephrosis subsequent to treatment is found also to indicate a poor prognosis in so far as eventual 5 year salvage is concerned.

Of 36 patients in whom the pretreatment pyelograms showed hydronephrosis, there were 21 in whom the posttreatment pyelograms showed improvement. Of these, 9 or 42.9 per cent survived for more than 5 years. This is approximately twice the 5 year survival rate for the entire group of 67 patients in whom the pretreatment pyelograms showed hydronephrosis (Table III). In the 15 patients whose posttreatment pyelograms showed no improvement, only 2 or 13.3 per cent survived for more than 5 years (Table V).

Value in determining recurrence or persistence of carcinoma

This group of 295 patients has also been studied for another purpose which has been made the subject of another report, namely, an attempt to find criteria for early detection of failure of irradiation therapy so that any suitable patient may be given the benefit of radical operation as soon as possible. An attempt has been made in this study to determine whether the urology studies have afforded any assistance in this regard.

There were 37 patients with proved recurrence or persistence of carcinoma. In 28 of these patients pretreatment pyelograms

Table VI. Urinary tract status in relation to radioresistant carcinoma of the cervix

	Proved carcinoma	Suspected carcinoma (88% later proved)	Clinically well
Total patients	37	39	77
No. with pre- and posttreatment pyelograms	28	24	36
Pyelograms unchanged	13 (46.4%)	17 (71.0%)	34 (94.4%)
Increased dilatation	10 (35.7%)	4 (16.6%)	1 (2.9%)
Decreased dilatation	5 (18.0%)	3 (12.5%)	1 (2.9%)
Living and well 5 years	12.1%		68.8%

had been obtained. In 13 of these the post-treatment pyelograms were unchanged, in 10 there was increased hydronephrosis, and in 5 the pyelograms showed improvement. Of this group only 5 patients have survived for 5 years, and each of these was subjected to radical operation within 2 months of the first suspicion of recurrence.

Table VII. Fistulas according to stage of carcinoma

Stage	Patients treated	Living and well 5 years		Fistulas (all types)	
		No.	%	No.	%
I	76	52	69.7	2	2.6
II	130	51	39.4	10	7.6
III	70	15	21.1	10	14.3
IV	17	0	0	2	11.7
Total	295	128	43.4	24	8.1

In another group of 39 patients persistence or recurrence of carcinoma following irradiation was not proved immediately, but eventually 88 per cent of them showed carcinoma. Twenty-four of these had been studied by both pretreatment and posttreatment pyelograms. In 17 of these the pyelograms were unchanged; 4 showed increased hydronephrosis, and 3 showed improvement.

There were available pretreatment and posttreatment pyelograms in 36 of 77 patients in whom there was no suspicion of recurrent or persistent disease. In 34 of these the pyelograms showed no change following treatment, while there was increased hydronephrosis in one patient and improvement in one other. These data are shown in Table VI.

This group of patients is too small to be statistically significant. The findings, however, are suggestive that the acquisition or increase in hydronephrosis following completion of treatment should arouse strong suspicion of recurrence or persistence of carcinoma. On the other hand the persistence of normal pyelograms and even improvement in the pre-existing hydronephrosis does

not rule out the presence of radioresistant cancer.

The pyelographic and cystoscopic study of patients at the time of discovery of radioresistant cancer are helpful in the selection of possible surgical procedures. At times such studies may indicate a hopelessly advanced stage of disease, making operation inadvisable. If there is evidence of bladder involvement or even close proximity to the bladder as indicated by massive edema of the base and trigone, exenteration rather than the radical Wertheim procedure should be the choice.

Fistulas

In Table VII may be seen the 5 year survival rate for the four stages of invasive carcinoma and also the incidence of all types of fistulas as distributed among patients with these four stages of disease. This

Table VIII. Relationship of appearance of fistulas to stage of carcinoma and treatment

Stage of carcinoma	Died less than 1 year	Lived more than 1 year
I	1	1
II	6	4
III	9 (1 lost, advanced carcinoma)	0
IV	2	0
Total	18	5 (1.4%)

includes all fistulas, and in the 12 patients with fistulas in whom the disease had been in Stages III or IV there was persistent carcinoma of the cervix in all. We have felt, however, that the mere existence of persistent carcinoma at the time the fistula occurred did not necessarily preclude the fistula's having resulted from irradiation. Arbitrarily, we have assumed that, if the patient died in less than one year after the appearance of the fistula, the fistula probably resulted either from cancer or from a combination of cancer and irradiation. If, on the other hand, the patient survived more than one year from the date of dis-

covery of the fistula, we have felt that the fistula probably resulted from treatment alone. The data in this regard are shown in Table VIII.

From this table it is seen that there were only 5 patients in whom the development of a fistula could be exclusively attributed to irradiation therapy. This is an incidence of less than 1.4 per cent, which compares quite favorably with the 9 per cent or more usually following treatment by radical operation.

Comment

In choosing the title for this paper we have meant to indicate that our purpose has been not to report merely further statistics on urologic complications following irradiation therapy but to study this last series and by comparing it with former ones to determine to our own satisfaction if these studies have been of worthwhile value in the management of this disease. It seems evident from all of our studies that abnormalities such as hydroureteronephrosis discovered in pretreatment pyelograms are strongly suggestive of a poor prognosis. Furthermore, the development of or increase in hydronephrosis subsequent to treatment may be an indication of persistent or recurrent cancer and therefore further indication of a poor prognosis. Occasionally, the pretreatment cystoscopic examination of the bladder may disclose unsuspected carcinomatous invasion in this viscus and thus lead to classification of a case as Stage IV which without such examination might have been classed in an earlier stage. This point we have never analyzed statistically, but it occurs frequently enough to warrant some emphasis.

Another purpose in these studies has been to determine if possible what factors in the techniques of irradiation therapy might lead to complications and thereby to be able to eliminate them in so far as possible. At the time of our 1949 report we became convinced that the factor of greatest importance was the intensity of radium therapy.

We are sure that complications occur much less frequently when the intensity is relatively low than when it is high. Our present technique is one of relatively low intensity. If we consult Table II we find that in this group of patients there were 11 in whom posttreatment studies showed evidence of hydronephrosis not present in the pretreatment studies. From Table VI, however, we find that all but one of these patients fell into the groups with either proved or suspected persistent or recurrent carcinoma, so that in only one could this type of complication be attributed to the therapy. In addition to this one patient there were 4 who developed ureteral strictures without associated hydronephrosis. The incidence of such complications in the group reported in 1939 was 15 per cent, and those patients were all treated by a high intensity method of radon administration, but the total dosage was considerably less than our present 4,800 mg. hr. of radium. We believe, therefore, that as a result of our continued study of this subject we have practically eliminated ureteral stricture and hydronephrosis as complications attributable to irradiation. We have been less fortunate with fistulas, but their incidence is being reduced gradually.

At the time of the 1956 report we expressed an intention to study dosimetry in an effort to further reduce complications, but, because of certain technical factors unforeseen at that time, the efficient carrying out of this intention has not been possible. With extreme care in the location of radium, however, and careful attention to all details of roentgen therapy, the incidence of complications has been further reduced. At the present time x-ray examinations to check the location of the radium are being taken immediately after each application. Radium is removed and reapplied as indicated by these positioning films. It is our hope that this will further reduce the incidence of complications.

At the time of our 1939 report we reviewed and analyzed a considerable number of reports on this subject, but as the years have passed pertinent articles have appeared

with decreasing frequency. This has been disappointing to us. We had hoped that our continued interest would have stimulated similar studies in other clinics. Perhaps the explanation lies in the fact that our female urologic clinic is an integral part of the gynecologic department.

Conclusions

We believe that a comparison of the study of this group of patients with the several other groups previously reported justifies the following conclusions:

1. Pretreatment excretory urography and cystoscopic examination of the bladder reveal information of considerable value in predicting prognosis and at times in accu-

rately determining the stage of carcinoma of the cervix.

2. Similar studies at varying intervals following the completion of treatment give further aid in predicting prognosis, and at times afford the first clue to suspected recurrence or persistence of carcinoma.

3. Urologic study of patients with radio-resistant cancer assists in the decision on the advisability of radical operation and on the type of such operation to be undertaken.

4. The long-range pursuit of these studies has indicated factors of irradiation technique which have tended to produce complications, and thus we have been able to eliminate such factors with a resultant marked reduction in the incidence of such complications.

REFERENCES

1. Hunner, G. L., and Everett, H. S.: J. A. M. A. 95: 327, 1930.
2. Hunner, G. L., and Everett, H. S.: J. Urol. 28: 333, 1932.
3. Everett, H. S.: AM. J. OBST. & GYNEC. 38: 889, 1939.
4. Everett, H. S., Brack, C. B., and Farber, G. J.: AM. J. OBST. & GYNEC. 58: 908, 1949.
5. Morton, D. G., and Kerner, J. A.: AM. J. OBST. & GYNEC. 57: 625, 1949.
6. Diehl, W. K., and Hundley, J. M., Jr.: Surg. Gynec. & Obst. 87: 705, 1948.
7. Kimbrough, R. A., and Muckle, C. W.: AM. J. OBST. & GYNEC. 56: 687, 1948.
8. Brack, C. B., Everett, H. S., and Dickson, R.: Obst. & Gynec. 7: 196, 1956.

Discussion

DR. F. BAYARD CARTER, Durham, North Carolina. Those of us who had the privilege of hearing Dr. Everett present his paper in 1939 before this Society will recall his discussion of the use of high intensity radon treatment to the cervical cancers. In that paper he stressed the high incidence of urologic complications. He pointed out at that time that hydronephrosis found in patients before treatment was a grave prognostic sign.

This first study led to changes in the methods of irradiation therapy under Dr. Brack, and these methods are detailed in the present paper. The combination of radium and x-ray therapy as described was calculated to deliver approximately 20,000 r to the cervical canal, 8,000 r to Point A, and just less than 4,000 r to Point B. The authors note that in recent years an attempt has been made to increase the dose at Point B by increasing the external x-ray therapy.

We would give complete approval of the authors' insistence that the patient with cancer of the cervix should have thorough urologic studies before treatment and regularly during the years of survival. In fact, these studies are mandatory as are the bone surveys and the studies of the bowel.

In 1949, before this Society, Everett and Brack gave a paper in which they concluded that with the lower intensity method of radium administration the incidence of serious urologic complications in patients who had survived 5 years or more was reduced to an almost negligible minimum. They stated, however, that an increase in radium dosage from 4,800 to 6,000 mg. hr., by increasing the amount of radium from 100 to 125 mg., administered with exactly the same time factors, led to a high incidence of serious complications. Time for my discussion does not permit adequate review of the authors' 1956 paper.

The gist of this report is that "295 patients with all stages of cancer" were treated during the years 1949 to 1953. The survival for 5 years or more was 43.4 per cent. The incidence of complications in these 295 patients, including those who did not survive 5 years, was 16.9 per cent. The incidence of complications in those patients who had survived 5 years or longer was 10.7 per cent. This figure was definitely lower than was the figure for the complications in the patients of the 1943 to 1948 group.

In the 1949 to 1953 group the urologic complications totaled 33 (11.2 per cent). Of the 295 patients 215 had pretreatment pyelograms; 148 showed normal pyelograms and the 5 year survival rate was 70.3 per cent. Sixty-seven patients whose pretreatment pyelograms showed hydronephrosis had a 5 year survival rate of 22.4 per cent.

It is important to note that the authors stress the fact that 31 patients with Stage I or Stage II cancers showed pretreatment hydronephrosis. The clinical staging of the cancer, in our opinion, should not influence the performance of urologic studies.

The authors combine their present statistics with those of their 1956 report and present an 11 year statistical summary for the years 1943 to 1953. In 99 patients with normal pretreatment pyelograms, the pyelograms remained normal in 77, and 61 (79 per cent) remained well for more than 5 years. In 22 patients who developed evidence of hydronephrosis after treatment, only 6 (27.3 per cent) survived for more than 5 years.

There were 36 patients in whom pretreatment pyelograms showed hydronephrosis, and 21 of the posttreatment pyelograms showed improvement. Nine (42.9 per cent) of these 21 patients survived for more than 5 years.

Much discussion is indicated of the authors'

section on the value of urologic studies in determining recurrence or persistence of carcinoma. Although their group of patients is too small to be significant statistically, we can agree with their statement, "the acquisition or increase in hydronephrosis following completion of treatment should arouse strong suspicion of recurrence or persistence of carcinoma." We would agree also with their statement that "the persistence of normal pyelograms and even improvement in the pre-existing hydronephrosis does not rule out the presence of radio-resistant cancer."

In their analysis of fistulas they show a total of 24. Ten occurred in Stage III cancers and 2 in Stage IV cancers. In 130 Stage II cancers 10 (7.6 per cent) fistulas were found, and in 76 Stage I cancers 2 (2.6 per cent) fistulas were found. In only 5 patients was it considered that the development of the fistulas was due exclusively to irradiation therapy.

With their conclusions we can agree. The urologic studies, the bone surveys, the bowel studies are all an integral part of the complete work-up of any patient with any stage of cervical cancer. Whether the patient is to be treated by accepted irradiation techniques or by extensive operative procedures or by a combination of irradiation and operation or by operation and irradiation, these studies should be complete.

They are also mandatory in the follow-up of posttreatment course and survival studies. Many patients seen in our clinic, who have been told their cancer has been "cured," have not had these studies. Many have "residual" or "persistent" cancer. Many show the changes in bladder, ureter, and kidney which constitute poor prognostic signs. Some patients, who at necropsy show no evidence of residual cancer, have died as a result of the changes in the urinary tract which the authors emphasize.

Results of early repair of vesicovaginal fistula with preliminary cortisone treatment

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IN 1952 we reported our results with cortisone in the treatment of ligneous cellulitis of the pelvis.¹ The efficacy of this form of therapy in this disease has been confirmed by others.⁵⁻⁸ Because of similarity of tissue reaction in ligneous cellulitis of the pelvis and that found in areas surrounding vesicovaginal fistulas, we decided to utilize cortisone in the latter entity. This was done to ascertain whether or not early resolution of indurated and brawny areas could be accomplished in cases of vesicovaginal fistulas as had been observed in pelvic ligneous cellulitis. Furthermore, a common finding in both disease entities prior to the use of cortisone was that at least 4 to 6 months' time was required before resolution or beginning resolution of the inflammatory process occurred. Therefore, we reasoned that if cortisone could produce the same striking results as regards resolution of inflammatory reaction in cases of vesicovaginal fistulas as it did in ligneous cellulitis, early repair of

vesicovaginal fistula with reasonable assurance of successful closure might be effected.

This would be of considerable advantage as a period of no less than 4 months and usually of 6 months between discovery and repair is recommended as standard practice.^{3, 4}

Since February, 1953, we have routinely used cortisone in the preoperative management of vesicovaginal fistulas where induration existed about the fistula. A preliminary report on our first 9 cases was presented in 1957.² Since that time 15 additional cases have been so treated. These 24 cases form the basis of this report.

Material

For purposes of definition and clarity we have divided the cases in this series into two main categories, namely, acute and chronic. Acute cases are defined as those in which the time lapse from discovery of the fistula to repair did not exceed 8 weeks. In all cases the fistula was discovered within 7 days to 2 weeks after delivery or operation for benign or malignant uterine disease. There had not been any previous attempt at surgical repair of the fistula. Twenty cases comprise this group, 16 of which were operated within one month and 4 within 8 weeks of discovery of the fistula (Table I). Of course, any delay longer than 2 weeks from discovery of the fistula to repair was due to the

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Table I. Time interval between discovery of fistulas and repair in acute cases

<i>No. weeks</i>	<i>Benign*</i>	<i>Malignant†</i>
2	3	1
3	3	2
4	5	2
5	1	
6	0	
7	2	
8	1	
4.5 (average)	15 (total)	5 (total)

*Followed therapy for benign lesions.

†Followed therapy for malignant lesions.

Table II. Etiology of fistulas

	<i>Acute</i>		<i>Chronic</i>	
	<i>Benign</i>	<i>Malignant</i>	<i>Benign</i>	<i>Malignant</i>
Obstetric	3			
Surgery	12		3	
Radiation and surgery		5		
Radiation				1
Total	15	5	3	1

fact that the referring physician or agency did not send the patient to us immediately. In all 20 of these cases attempt at repair was effected within 2 weeks of the time we first observed the patient.

By chronic cases we mean those in which the time lapse from discovery of the fistula to repair exceeded 4 months and in which there was induration of such extent that immediate repair, without preliminary cortisone therapy, was not advisable. Since cortisone was used by us in such cases they are included in this report. Some had previous attempts at repair elsewhere without preliminary cortisone therapy. Four cases constitute this group, 3 of which were the result of operation for benign lesions and one of which followed radiation therapy for carcinoma of the cervix.

Thus, from February, 1953, to May 1, 1960, there have been 24 cases of vesicovaginal fistulas managed on our service in which cortisone was utilized preoperatively. Seventeen of these patients were admitted to

the Tulane Unit, Charity Hospital, and 7 were private patients referred to the senior author. Obstetric injuries accounted for 3 of the fistulas. Radiation therapy was responsible for one. A combination of complete radiation, extensive (radical) hysterectomy, and pelvic lymphadenectomy for cancer of the cervix was the etiological factor in 5 instances. In the remaining 12 cases, the fistula followed total hysterectomy for benign disease (Table II). All of the fistulas resulting from a combination of radiation and operation occurred on our service. The majority of the others were in patients referred to us for therapy. The fistulas varied from 2 mm. to 5 cm. in diameter (Table III).

Method

As soon as a patient with a vesicovaginal fistula is encountered a retention catheter is placed in the bladder and 100 mg. of cortisone is administered orally, three times daily for 10 to 12 days. At the end of that period of time the catheter is removed. In many patients where the fistula develops within the first 14 preoperative days, spontaneous closure occurs with the sole aid of catheter drainage. We do not mean to imply that the addition of cortisone will result in a higher percentage of spontaneous cure, nor do we believe that the addition of this drug will result in a lower percentage of spontaneous cure. Certainly on our service the addition of cortisone in cases of accidental injury to the bladder at the time of operation has not been followed by a decrease or an increase in the number of patients who develop fistulas requiring surgical correction. Cortisone is administered for the sole purpose of having the patient ready for immediate operation if

Table III. Sizes of fistulas

<i>Size (cm.)</i>	<i>No.</i>
Less than 1	4
1-2	6
2-3	6
3-4	6
4-5	2

catheter drainage fails to effect cure. Thus, the time element from occurrence of fistula to corrective operation is reduced. During the period that cortisone is administered, antibiotics are also prescribed to cover any "cortisone spread effect." In addition, cultures of the urine and sensitivity tests are obtained. This is performed so that specific antibiotics for specific organisms can be available postoperatively.

In every case the fistula was repaired by means of the vaginal approach with the patient in the lithotomy position. Counter drainage either in the form of suprapubic drainage or vaginal cystostomy was not employed. Relaxing incisions, tidal irrigation, or constant suction applied to the catheter was not used. The patient was not, following operation, placed on her abdomen or on a Bradford frame.

Suture material utilized was 2-0 or 3-0 chromic catgut. In the first 5 cases in this series a single purse-string suture in the muscularis of the bladder was the method of closure. No sutures were placed in the mucosa of the bladder or vagina. This method was used because we wished to prove that the condition of the tissues is the most important factor in early repair. Also, it has been stated "it is known that it is faulty to use the purse-string method."³ Thus, in using a method of suture that had been condemned and by not placing sutures in the mucosa of the bladder or vagina, we deliberately avoided some of the accepted dictums and placed our confidence in the ability of cortisone to return tissue to normal or near normal so that any method of suture would be successful. The same method of closure was used in one other case. In the remainder of the cases the fistula was closed by means of interrupted sutures in the muscularis of the bladder and vaginal mucosa. This is the method we prefer. Furthermore, all fistulas are not amenable to purse-string closure. Also, we realize that closure of the vaginal mucosa materially adds to the chances of success. However, to reiterate, we had a point to prove and to do so, of necessity, we had to rely on one suture placed in the

muscularis of the bladder. In all cases we employed wide dissection about the fistulas, in order that suturing with minimum tension would be possible.

Postoperatively, the majority of the patients were ambulated within 24 to 48 hours. The distal end of the retention catheter was placed in a jug or plastic bag which the patient carried. The patients were taught to irrigate the catheters with 1 oz. of sterile water. This was performed by the patient every 2 hours. They were cautioned that if any difficulty at all was experienced when they irrigated the catheter, the senior resident or myself was to be called immediately. Thus, any possible damage by one inexperienced in catheter management was bypassed. No further attempt was then made to irrigate the catheter. It was removed and a new catheter inserted. As a matter of fact, 3 of our more recent private patients were discharged from the hospital on the fourth postoperative day and they irrigated the catheters at home. In each case the catheter was removed in our office on the twelfth postoperative day. In one instance one of the patients called and stated that she experienced difficulty in introducing the water into the catheter. She was told to go to the emergency room of the private hospital where the senior resident met her, removed the catheter, and replaced it with a new one. All healed without any complications. Estrogenic creams were applied by the patient twice daily to the vulva and introitus until the twenty-first postoperative day. No vaginal examinations were performed until 6 weeks after the operation, unless leakage of urine occurred.

Results in acute cases

As stated previously, 15 of the 20 acute cases were not associated with the therapy of malignant uterine disease. Thirteen of this group healed on the first attempt at closure (Table IV). Following repair and removal of the catheter, leakage of urine continued in one patient. The catheter was immediately replaced, cortisone again administered, and repair again performed 12 days later.

This time cure was effected. In another instance, early repair failed twice but success was achieved on the third attempt. In all, only 5 weeks elapsed from admission to the time of cure. Cortisone was used as described before each repair (Table IV).

Table IV. Results in acute fistulas in benign cases

Healed first attempt	13
Healed second attempt	1*
Healed fourth attempt	1†
Total	15

*Repaired again in one month—healed.

†Repaired three times in 3 months—healed.

Five of the patients in this acute group had been previously treated for Stage I or Stage II cancer of the cervix. Radiation in dosage of approximately 6,000 r to Point A and 2,600 r to point B had been administered. Following radiation therapy operation was employed for recurrence. The surgical procedure consisted of extensive (radical) hysterectomy and pelvic node dissection. Following operation, vesicovaginal fistula developed. Thus, these cases differed from the other 15 in that full radiation preceded operation. Here we were dealing with tissues that were affected by radiation in addition to changes occasioned by the fistula.

In all, cortisone produced regression of swelling and edema and easy dissection and suture. In 2 cases successful closure was accomplished. In one, two attempts in a 9 week period resulted in failure. In a case of rectovaginal fistula, failure resulted. The patient died from septicemia on the fourteenth postoperative day. Three days before death leakage of urine occurred (Table V).

Results in chronic cases

As previously stated the chronic cases were those in which more than 4 months' time had elapsed from the discovery of the fistula to the attempt at repair. However, all of these patients showed marked induration about the fistula, and we did not believe the tissues were in any condition for us

to attempt repair. Therefore, cortisone therapy was employed for 10 days and the patient operated upon. As in the acute cases, resolution of the induration about the fistula was attained. There were 4 patients in this group. In 3, the fistula resulted from operation for benign disease. One had a rectovesicovaginal fistula of 18 months' duration. Closure of both fistulas was successful on the first attempt. Another had a vesicovaginal fistula of 5 years' duration, with the last attempt at repair in July, 1957. After preliminary cortisone therapy, successful repair was performed in December, 1957. A third patient with vesicovaginal fistula of 61 weeks' duration was given preliminary cortisone therapy and operated on in December, 1958. She returned in August, 1959, complaining of sporadic leakage of urine. A small pinpoint-sized fistula was discovered. Again, preliminary cortisone was utilized and repair resulted in successful closure. The last case in this group is that of a large 5 cm. rectovesicovaginal fistula which followed

Table V. Results of acute fistulas in 5 patients with cancer

No. of attempts	Time (weeks)	Outcome
2	4 and 9	Failure
1	3	Success
1	3	Success
1	4 (also rectovaginal)	Failure*
1	2	Failure†

*Died on fourteenth postoperative day, septicemia.

†Since presentation of this paper this patient has been operated upon again and is cured.

Table VI. Results in 4 cases of chronic fistula

Type of fistula	Time	Outcome
<i>Benign</i>		
Rectovesicovaginal	18 months	Success
Vesicovaginal	61 weeks	Success
Vesicovaginal	5 years	Success
<i>Chronic</i>		
Postradiation rectovaginal and vesicovaginal	2 years	Failure

radiation therapy for carcinoma of the cervix. This patient was first seen 2 years after the occurrence of the fistula. Colostomy and cortisone therapy produced the desired changes in the tissues. However, despite the attempts at closure, the fistula is still present and a Bricker pouch will be necessary to afford relief (Table VI).

Comment

Cortisone administered for a period of 10 to 12 days, in doses of 100 mg. three times daily, was successful in producing regression of induration about vesicovaginal fistulas. Involved tissues returned to a stage where dissection of tissue planes was easily accomplished. Furthermore, sutures did not cut through the tissues when introduced or tied, and easy approximation of structures was accomplished. In 15 cases of fistula resulting from obstetric injury or surgical therapy for benign disease, 13 were successfully closed on the first attempt at early repair. In the other 2 cases, as soon as failure was realized cortisone was readministered and the patient reoperated upon as described previously. These results are considered by us to be excellent. In the chronic cases that followed therapy for benign disease preliminary therapy with cortisone again resulted in resolution of the indurated areas and allowed for easy repair. The results here were good. Of course, during this period of study other cases of vesicovaginal fistulas were observed and treated that fall into this chronic group. In these latter cases, however, when first seen, there was no induration of tissue about the fistulas and consequently there was no need for preliminary therapy with cortisone. It is re-emphasized that in vesicovaginal fis-

tula of long standing we utilize cortisone only if induration is still present about the fistula.

In the cases associated with previous extensive operation and/or radiation therapy for cancer of the cervix the results were not as good. Only 2 of the 6 fistulas remained closed on the first attempt. In 2 of the failures rectovesicovaginal fistulas existed. It is significant, however, that tissues that had been exposed to extensive operation and/or radiation reacted to cortisone as in the cases where radiation had not been utilized. It is readily admitted that cases of radiation therapy for cancer of the cervix followed by extensive (radical) hysterectomy and pelvic node dissection, if followed by vesicovaginal fistula, produce a situation not easily repaired, whether early or late.

Conclusions

1. It is not necessary to wait 4 to 6 months or more from the time of discovery of a vesicovaginal fistula to the time of repair.
2. Cortisone, 100 mg. three times daily for 10 to 12 days, will effectively reduce the induration in tissue surrounding the fistula and allow for immediate repair.
3. Repair will be successful in the majority of acute cases where the fistula has resulted from birth trauma or operation for benign disease.
4. In cases associated with previous radiation and extensive (radical) operation for cancer of the cervix, immediate repair can be accomplished, but the results are not so good as when early repair is performed in nonirradiated cases.
5. No ill effects of any nature from the use of cortisone have been noted in our cases.

REFERENCES

1. Collins, C. G., Davidson, V. A., and Mathews, N. M.: *New Orleans M. & S. J.* 104: 389, 1952.
2. Collins, C. G., and Jones, F. B.: *Obst. & Gynec.* 9: 533, 1957.
3. Counseller, V. A., and Haigler, F. H.: *Am. J. OBST. & GYNEC.* 72: 367, 1956.
4. Everett, H. S., and Mattingly, R. F.: *Am. J. OBST. & GYNEC.* 72: 712, 1956.
5. Hurtig, A.: *Canad. M. A. J.* 72: 123, 1955.
6. Peerman, C. G., Jr., and McGanity, W. J.: *South. M. J.* 50: 374, 1957.
7. Wills, S. H., Jacobs, W. M., and Lauden, A. E.: *Obst. & Gynec.* 7: 689, 1956.
8. Wills, S. H., Jacobs, W. M., Lauden, A. E., and Fromhagen, C.: *Obst. & Gynec.* 11: 112, 1958.

Discussion

DR. NORMAN F. MILLER, Ann Arbor, Michigan. Since Dr. Collins' earlier report on the use of cortisone as a means of reducing induration prior to repair of vesicovaginal fistula, I have hoped we might encounter cases where such preliminary treatment seemed necessary. Up to the present time no such encounter has occurred, due, probably, to our own peculiar interpretation of what constitutes suitability.

I have not had experience with the adrenal steroids as part of preliminary preparation for operation of vesicovaginal fistula cases. Rather, I have the temerity to discuss this paper on the basis of a moderately extensive experience in the surgical correction of these lesions.

Dr. Collins uses 300 mg. of cortisone daily for 10 to 12 days for the reduction of induration, and I quote: "Cortisone is administered for the sole purpose of having the patient ready for immediate operation if catheter drainage fails to effect cure." If catheter drainage is instituted in suitable cases in hope of obtaining spontaneous healing, I wonder if 10 to 12 days is long enough. The fact that in Dr. Collins' cases the average time lapse between discovery of the fistula and repair was only 4½ weeks is indeed impressive. In our experience without the use of cortisone there is customarily a lapse of 8 to 12 weeks before operation is undertaken. However, we have not in the past considered this too long, since recovery time is needed from the event leading up to the fistula.

Dr. Collins has demonstrated that the preoperative use of cortisone does not interfere with healing and he makes no claim that cortisone improves the primary cure rate. His statistics bear this out. Of 15 acute cases occurring after operation for benign lesions, 13, or 80 per cent, healed per primam. This is good. It is also about par for the course. Among 5 chronic fistulas developing after operation and irradiation for cancer, 2 healed per primam, or about 40 per cent. These represent a difficult group. It would be an interesting and, indeed, convincing support for the use of cortisone as a preoperative measure if it is revealed that cortisone not only reduced the ligneous induration so common in these cases but also improved the blood supply to this devascularized area to the extent that the fistula proper could be closed.

In my experience with these postirradiation cases with or without previous radical operation, it has been necessary to drop down and close

the vaginal tube at a point where healthy tissue was available. Perhaps Dr. Collins will indicate at what point he closes these fistulas. I endorse his use of very fine chromic catgut. We also believe in early ambulation.

The fact that some of his patients have been instructed in self-irrigation of the in-lying catheter and are discharged 4 days after operation is an intriguing and perhaps justifiable alteration in what might otherwise be an expensive hospital stay. However, I am not yet ready to depend on the patient's self-care and catheter irrigation for any but those with small fistulas.

Cortisone in the dosage of 300 mg. for 10 to 12 days could activate latent tuberculosis. Apparently this did not occur in any of Dr. Collins' cases.

The essayist takes the precaution of using antibiotics. Does he favor preoperative use of estrogen, especially in castrated patients, in order to augment local epithelial activity and perhaps blood supply?

DR. ANDREW A. MARCHETTI, Washington, D. C. Any approach to reduce successfully the time which elapses between the disclosure of a vesicovaginal fistula and its repair should be considered commendable. It is obvious that no one could appreciate it more than the patient. Dr. Collins and his co-workers have concluded that it is possible to reduce this period of waiting 4 to 6 months by administering immediately preoperatively a course of cortisone treatment as soon as the fistula is diagnosed.

A comment upon the over-all results should be made. There were 6 instances in which fistulas were diagnosed in patients who had been treated for genital carcinoma by irradiation and extensive operation. It is not surprising that among these cases the results, after treatment and repair, were successful in only 2 instances. Even under the best auspices we are aware that the soundness and integrity of the tissue is compromised in such cases and, hence, the results unpredictable.

On the other hand, among the cases in which the fistula resulted from procedures used to treat benign disease, in the 15 cases classified as acute, early repair according to the authors' technique produced primary successful results in 13 cases. Among the 2 primary failures, one required a second attempt and the other a fourth attempt before the desired result was obtained.

This comes close to an 85 per cent primary success rate.

It is my feeling that unless those of us who choose to wait 6 months before attempting the repair of a vesicovaginal fistula currently can show a better incidence of success, the approach recommended by Dr. Collins has real merit and should be tried.

DR. JOHN L. MCKELVEY, Minneapolis, Minnesota. Dr. Collins has apparently listed among the "malignant disease fistulas," those which were the result of operation on patients with malignant disease. Is this correct? Is it fair to assume that he does not advocate immediate repair of fistulas which appear during the course of irradiation therapy for malignant disease? Most of us have considered it wise to leave these alone for 2 years and until there is histologic proof of the absence of cancer in the area of the fistula. The fistula is a disaster under these circumstances but stirring up the growth of malignant tumor by surgical trauma may be even worse. Does he believe that recently irradiated tissue in the absence of histologic proof of tumor can be made to heal adequately following surgical repair?

DR. D. ANTHONY D'ESOP, New York, New York. In an unpublished study of our experiences with vesicovaginal fistulas, one of the very disconcerting end results among the obstetrical fistulas was that we found patients who were anatomically cured but had a great deal of functional disturbance with urinary control. Their injuries had been located at or near the vesical neck. The chance of having a poor result of this kind increased with the number of operations that had been previously performed, which suggested that scar tissue in the sphincteric area interferes with a good functional result. This would lead one to believe that a fistula should be repaired, if possible, before a great deal of scar is laid down. Certainly in the traumatic injuries of the bladder that we encounter in both abdominal and vaginal gynecologic surgery, immediate closure usually results in a cure without residual fistula.

With this experience in mind, we have more recently treated obstetric bladder injuries during the immediate postpartum period. We have had 3 patients with large defects repaired at 2, 2½, and 3 weeks post partum. These were treated with antibiotics and catheter drainage before

operation. Healing took place without incident in all three. At the end of about 2 weeks the edema that is incident to the trauma of delivery has disappeared; the tissues are dissectable in layers and can be approximated nicely without tension.

This is a small experience but sufficiently gratifying to make us continue to repair these fistulas early. It is not so much to save time as to avoid the scar tissue that is bound to form if these lesions are allowed to go for months before they are repaired. I agree that the rule about waiting 6 months before repair should be changed.

DR. HOUSTON S. EVERETT, Baltimore, Maryland. Four or 5 years ago we reported on a large series of fistulas before this Society, 65 of which were from surgical injury and only 9 of which had occurred in our own clinic. The others came in from outside, mostly from smaller communities where the operation had been performed usually by a general surgeon. Many of these patients had had numerous—up to as many as 10—unsuccessful attempts at repair in rapid succession before we saw them. This sort of thing does occur and I have been looking forward to hearing Dr. Collins' paper.

DR. COLLINS (Closing). Dr. Miller, I did not notice any alteration in the circulation. As to the use of estrogens, we use them postoperatively and not preoperatively but there is no reason why we cannot use them both times. We apply them to the vulva in the form of cream. In one case only, and that is the last one that broke down, did we use part of the vagina to close the fistula. The patient has a small leaking point on the side. In the other cases with radiation and operation we closed them as we do the acute cases.

As to the catheter care, I tell the patient that healing might depend on irrigation of that catheter; I suggest that she had better do it herself and that if the least bit of pressure is needed not to let anyone else try to force it. In the past I believe some fistula repairs have been broken down by people trying to force fluid into the bladder. I know nurses have been known to push a catheter through the urethra posteriorly.

Dr. Marchetti, we have used cortisone in rectovaginal fistulas. At first I had complete success with it, but in the past few cases we have not been so successful. We will keep on trying.

I want to emphasize that most of the rectovaginal fistulas we see are in connection with carcinoma.

Dr. McKelvey, the fistula in one patient treated by radiation only was 2 years old when she came to us. Whether we are going to spread carcinoma by releasing trapped cells I am not

sure, but we will attack the fistulas and close them as soon as we can. Of course, biopsy specimens are taken in cases of chronic fistulas. If the biopsy shows cancer then the fistula is not repaired, but pelvic exenteration is performed.

Detection of trophoblast in cord blood and fetal circulation

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THE bizarre behavior of trophoblastic tissue has been the subject of great interest since Schmorl described its deportation in 1893.¹ He noted the frequent presence of trophoblast in the lungs of patients dying of eclampsia.

Recently, Park² found multinucleated particles of tissue morphologically indistinguishable from syncytiotrophoblast in sections of lungs from 53 of 120 patients dying during pregnancy, parturition, or the puerperium. Bardawil and Toy³ reported similar findings in 57 of 109 cases from the Boston Lying-in Hospital.

Further studies in this area have recently been carried out by Douglas and associates.^{4, 5} They collected blood from the uterine vein, inferior vena cava, and antecubital vein during pregnancy and examined it for trophoblastic elements. Eight of 13 specimens obtained from the uterine vein and 3 of 33 from the inferior vena cava contained trophoblast. Eighty antecubital vein samples contained no trophoblastic elements. The immunologic significance of these findings in relation to the successful existence of pregnancy was discussed.

Transplacental migration of malignant cells from mother to fetus has been demonstrated indirectly by several authors. Friedrich,⁶ in 1866, reported a case of generalized carcinomatosis in a patient who gave birth to an infant with a similar type of growth on one knee. No malignant cells were found in the placenta. Berghinz⁷ in 1900, described transplacental metastasis to the fetus in a case of generalized lymphosarcoma. A case of Hodgkin's disease in mother and infant was reported by Priesel.⁸ Melanotic sarcoma in mother and fetus was noted by Weber and co-workers⁹ in 1930 and Holland¹⁰ in 1949. Examination of the placenta revealed melanotic tumor cells in a blood vessel of a chorionic villus.

This phenomenon of simultaneous maternal and fetal involvement also appears to be true of chorionepithelioma which is a primary placental neoplasm. MacRae¹¹ reported a case of chorionepithelioma in the mother, the infant being free of the disease. Choriocarcinoma occurring in both mother and fetus was described by Buckell and Owen¹² and Mercer and associates.¹³ However, the surprising finding of chorionepithelioma in the fetus when the mother revealed no evidence of the disease was reported by Emery¹⁴ in 1952 and by Kay and Reed¹⁵ in 1953. In both instances, the metastases were found in the liver and lung and the infants eventually died of the disease. These investigators were of the

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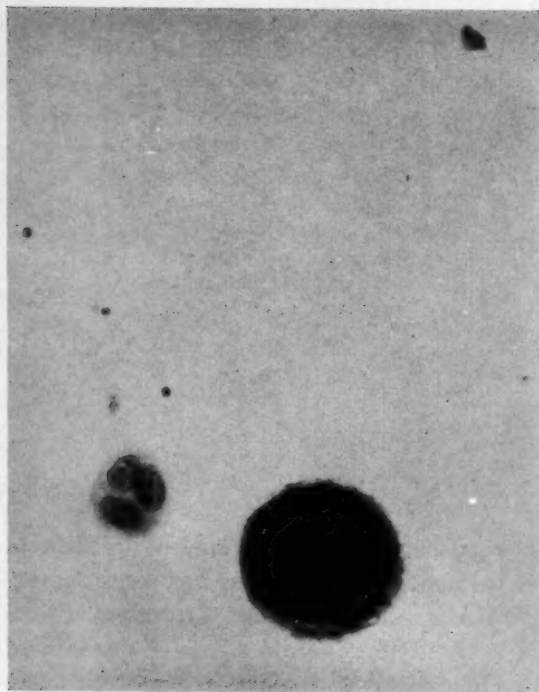


Fig. 1. Syncytiotrophoblast in direct smear obtained from placental surface of uterus at 8 weeks' gestation. ($\times 336$.)

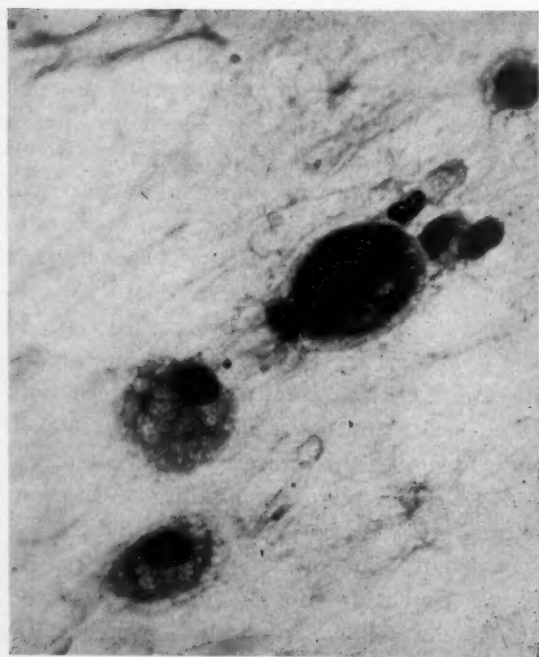


Fig. 2. Decidual cells in direct smear of endometrial surface of uterus at 8 weeks' gestation. (Original magnification $\times 798$.)

opinion that these tumors probably originated from teratomas rather than by transplacental migration of trophoblastic tissue.

To our knowledge no one has demonstrated the presence of trophoblastic cells in the fetal circulation. The present study was stimulated by this fact and by reports in the literature of chorionepithelioma occurring in the infant when the mother showed no evidence of the disease.

Material

1. Cord blood. Cord blood was obtained from 53 patients, selected at random, immediately following delivery. Care was taken not to contaminate the specimen with blood running down from the uterine cavity. An attempt was made to obtain the specimens before placental separation. All pregnancies and deliveries were uncomplicated except in one patient who had partial abruptio placentae. Of the 53 infants, 28 were females and 25 were males.

2. Fetal organs. Tissue sections from 25 consecutive autopsies performed on newborn infants who died 5 minutes to 10 hours after birth were examined for trophoblastic tissue. Stillborn infants were not included in the study because of the possibility of atypical cells resulting from autolysis.

3. Placental and decidual smears. In order to have a basis for comparison with known placental and decidual cells, direct smears were made from the placental and endometrial surface of a uterus at 8 weeks' gestation which was removed for therapeutic abortion. These smears were stained by the Papanicolaou method and used for reference in determining the cell type found in the cord blood samples (Figs. 1 and 2).

Methods

Two methods of examining blood specimens for tumor cells or trophoblast have recently been reported in the literature. Malmgren and associates¹⁶ described a technique using streptolysin and a millipore filter. The other, that of Sandberg and Moore,¹⁷ was used for this study with certain modifications.

Technique. Five milliliters of cord blood was mixed with 160 mg. of bovine fibrinogen dissolved in 4 ml. of normal saline containing 1 mg. of heparin. One hundred and sixty milligrams of fibrinogen were used rather than 80 mg. recommended by Sandberg because the smaller amount produced incomplete and slow precipitation of red blood cells in cord blood. After 10 to 12 minutes, the plasma layer was removed with a syringe and needle and centrifuged at 1,000 r.p.m. for 5 minutes. The plasma was then decanted and 4 to 6 smears were made from the concentrated mixture of remaining plasma and cells. These slides were fixed in 95 per cent alcohol and stained by the Papanicolaou method. The slides were

Table I. Trophoblasts and decidual cells in cord bloods

	<i>Trophoblasts</i>	<i>Decidual cells</i>
Positive	32	14
Negative	13	29
Questionable	8	10
Total	53	53

screened by the authors and a trained cytotechnologist. All atypical cells were marked and subsequently reviewed by each of the authors. The cells were classified as trophoblast, decidual or questionable. There was a tendency to underestimate the number of positive cells rather than classify questionable cells as either trophoblastic or decidual. Furthermore, the authors remained keenly aware of the ease with which the megakaryocyte can be confused with trophoblastic cells and great care was exercised in this regard.

Results

The results of the findings in 53 cord blood samples are summarized in Table I. Thirty-two of the 53 specimens revealed typical trophoblast cells (Figs. 3 and 4). There were 8 in which the cells were clas-

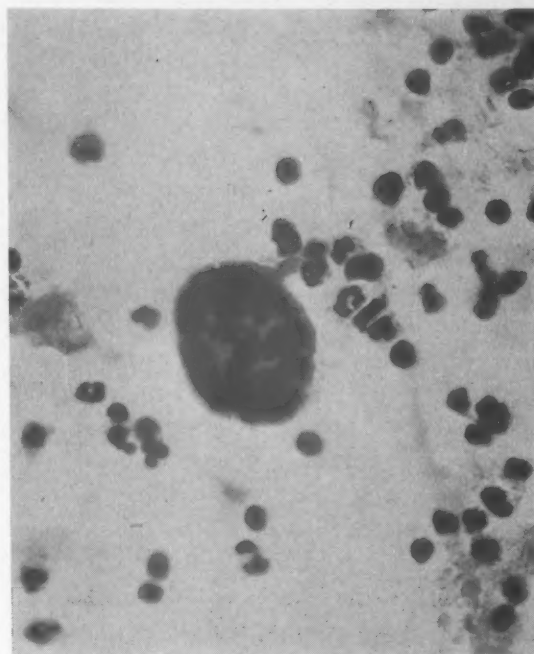


Fig. 3. Syncytiotrophoblast recovered from cord blood obtained at delivery. (Original magnification $\times 760$.)

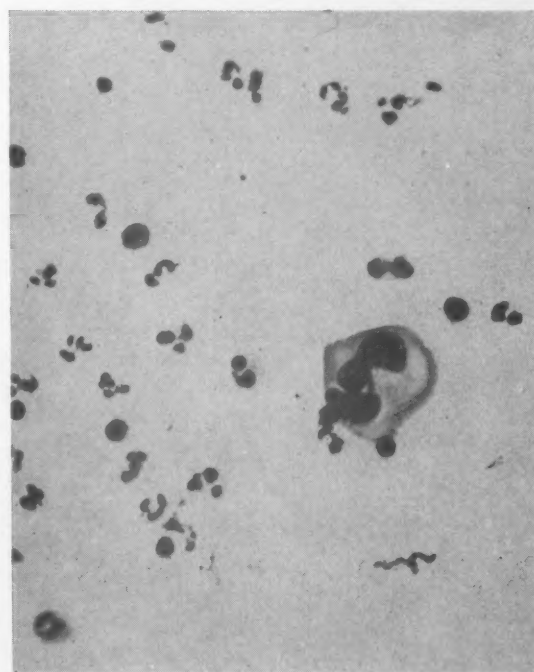


Fig. 4. Smaller trophoblastic cell recovered from cord blood obtained at delivery. (Original magnification $\times 640$.)

sified as questionable because they did not demonstrate the complete cytologic characteristics of trophoblast. Fourteen of 53 specimens contained cells typical of decidua (Fig. 5) and were cytologically identical with smears taken directly from the uterine cavity in early pregnancy. Again questionable cells were encountered which were not entirely typical of decidual elements. The incidence of trophoblast and decidual cells in cord blood was not related to the sex of the infant (28 females and 25 males). The umbilical cord blood obtained from the case of partial abruptio placentae contained both trophoblast and decidua-like cells.

The characteristic trophoblast cell is large, multinucleated, and easily found. Its size is usually in the range of 100 to 200 μ . The cytoplasm stains yellow or reddish orange and occasionally a brush border can be identified. The decidua-like cell is more difficult to find. As can be seen in Figs. 2 and 5, it is a much smaller cell, the cytoplasm stains a pale blue and the nuclear

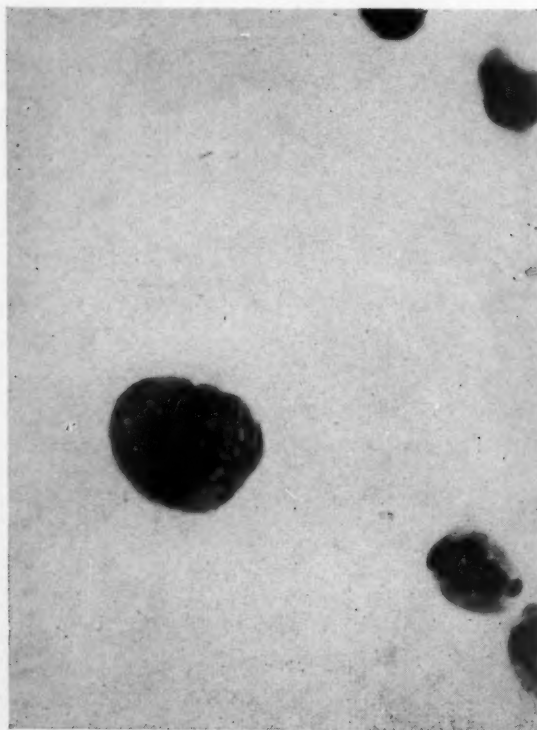


Fig. 5. Decidua-like cell found in cord blood obtained at delivery. (Original magnification $\times 1520$.)

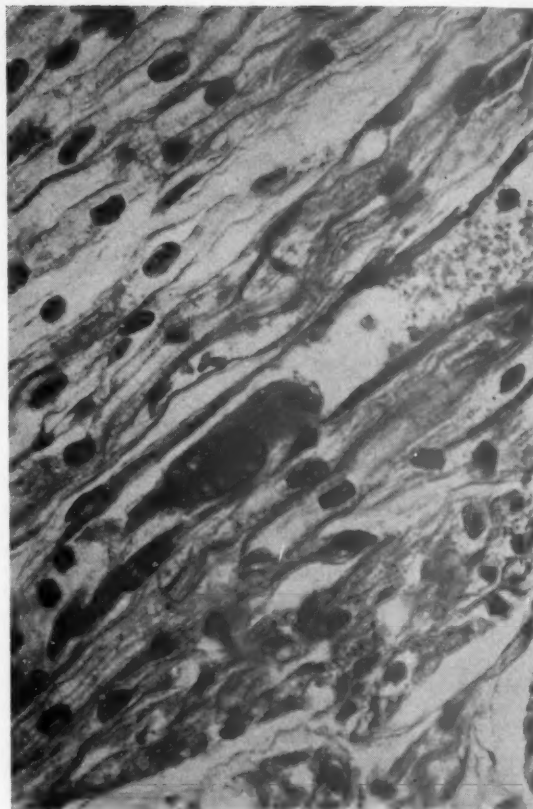


Fig. 6. Trophoblast in autopsy section of the heart of a newborn infant. (Original magnification $\times 798$.)

chromatin has a fine, granular pattern.

Because of the technique of precipitating the red blood cells with fibrinogen, it was felt that a significant number of trophoblasts were lost in the precipitate. Therefore, it seems safe to assume that there are probably more cells in the total blood specimen than were found in the supernatant plasma. No attempt was made at quantitative determination of these elements.

In order to further prove that trophoblasts and decidual cells enter the fetal circulation, tissue sections from autopsies performed on newborn infants were examined. Typical trophoblastic cells were found in a capillary of the heart from one fetus (Fig. 6) and in a sinusoid of the liver from another (Fig. 7). In the adrenal gland obtained from another newborn infant, cells having the characteristics of decidua were found in capillaries of the capsule (Fig. 8).

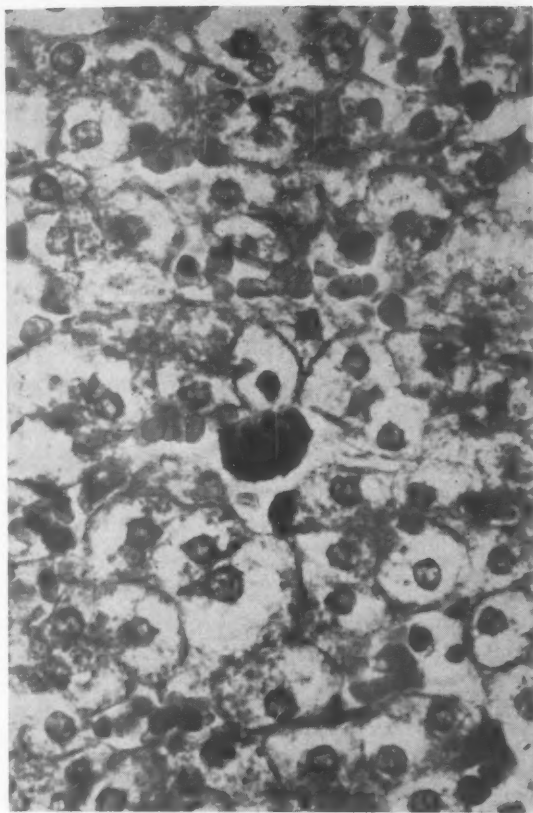


Fig. 7. Trophoblast in a liver sinusoid of a newborn infant. (Original magnification $\times 798$.)

The cells in the adrenal were identical with decidual cells found on direct smear of the endometrial cavity.

There may be some question as to the paucity of findings in autopsy sections. However, it must be kept in mind that these cells are carried to all parts of the body and their concentration in any one particular organ would consequently be minimal. Further explanation is evident in the physiology of fetal circulation. In the fetus the majority of blood coming from the umbilical vein enters the inferior vena cava via the ductus venosus and bypasses the liver. After entering the right atrium a large portion is diverted through the foramen ovale into the left atrium and thence to the peripheral circulation. The blood in the right atrium is pumped out through the pulmonary artery by the right ventricle. A small amount traverses the lungs but the major portion is

shunted through the ductus arteriosus into the aorta from whence it is also carried into the peripheral circulation. We believe that large numbers of trophoblastic cells are probably filtered out in the peripheral capillary bed before reaching organs such as the liver and lungs. Furthermore, as Thomas and co-workers⁵ demonstrated *in vitro*, trophoblastic tissue appears to be very susceptible to proteolytic enzymes and may be rapidly destroyed, thereby accounting for further diminution in the number of these cells in various organs. Park,² also reported the rapid destruction of trophoblastic tissue in rats after the injection of a placental emulsion.

Comment

The demonstration of trophoblastic elements in the fetal as well as the maternal

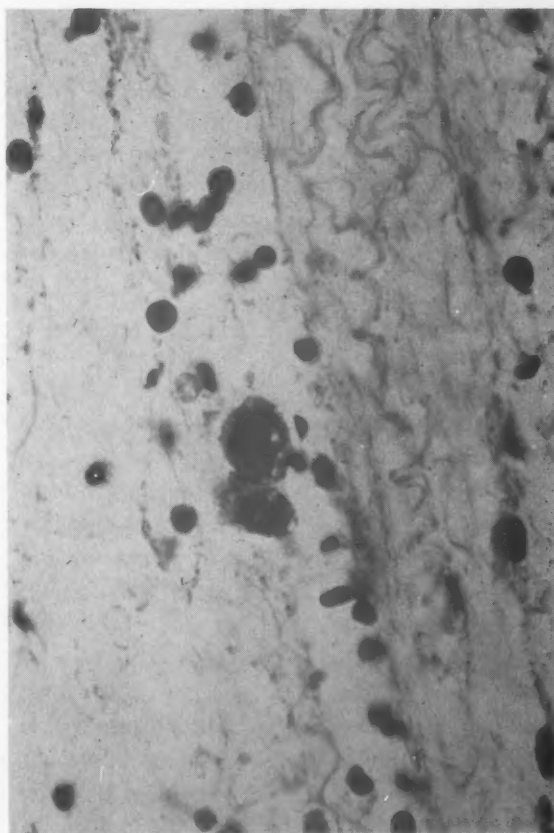


Fig. 8. Decidua-like cells in adrenal gland of newborn infant. Cells in capillaries of the adrenal capsule. (Original magnification $\times 798$.)

circulation makes it clear that these structures migrate in both directions from the placenta. This phenomenon is no doubt an accompaniment of normal delivery. Whether these cells pass into the fetal circulation only at the time of parturition or whether there is a continuous showering throughout pregnancy is very difficult if not impossible to determine with present-day techniques. Douglas and associates⁴ demonstrated that trophoblastic cells enter the maternal circulation during various stages of pregnancy. Syncytiotrophoblasts were detected in blood taken from the uterine vein in pregnancies of 18 and 22 weeks. We recently obtained blood from a broad ligament vein of a uterus containing a pregnancy of only 8 weeks' gestation. The specimen was drawn prior to any manipulation and contained numerous trophoblastic cells. It would appear, therefore, that there is early exfoliation of these elements into the maternal circulation.

The significance of trophoblast in the fetal circulation is open to wide speculation. It would appear that the so-called placental barrier is not a very effective one, but at most a highly permeable filter since cells 100 to 200 μ readily traverse it. This is true at least at the time of delivery if not earlier in pregnancy.

The question arises as to a possible beneficial role played by the exfoliated trophoblasts, perhaps through the transfer of various substances (endocrine, nutritional, immunologic) from mother to fetus.

The entrance of trophoblast into the fetal circulation offers a possible explanation for the occurrence of choriocarcinoma in the fetus when the mother is free of the disease. The question arises whether some inhibiting factor is present which prevents this type of malignancy in the mother when it is found in the fetus. Conversely, an inhibitor may prevent the development of choriocarcinoma in the fetus when the mother has the disease. Chorionepithelioma in males may also originate in this manner from dormant trophoblastic tissue implanted during fetal life.

Many instances of transplacental migration of malignant tumors to the fetus have been observed. A number of these cases reveal no evidence of placental metastasis. However, if cells the size of trophoblast (100 to 200 μ) can traverse the placenta, it is possible that tumor cells of practically all types may pass through into the fetal circulation without producing placental metastasis.

The migration of trophoblastic elements into the fetal as well as maternal circulation raises many questions as to the immunologic significance of this phenomenon. There is at present much speculation as to the mechanism which allows a pregnancy to continue. It is well known that successful grafting between 2 individuals is possible only in the case of monozygotic twins. If these criteria are not met, the homograft is destroyed. Since the genetic derivation of the fetus and placenta is different from those of the maternal host, it would appear that some factor is present which prevents the pregnancy from being destroyed in the same manner as a homograft.

Several explanations for the successful maintenance of a pregnancy warrant consideration. As stated by Douglas these tissues may be so embryonic that they are incapable of eliciting any type of antigenic response. He also discusses the possible development of tolerance by the maternal host to the conceptus as a result of the continuous showering of trophoblast into the maternal circulation. The detection of trophoblast in the maternal circulation at 8 weeks' gestation (which we have noted) certainly supports this latter theory. A desensitization type phenomenon may take place as a result of the "inoculation" of the maternal host with small amounts of syncytiotrophoblast beginning very early in pregnancy.

Another interesting possibility is suggested by the work of Billingham, Brent, and Medawar,¹⁸ in which tolerance to homografts was induced in animals by the prior injection of the donor's cells into these animals in utero or shortly after birth. It is conceivable that a similar tolerance is

accomplished in humans by the entrance of trophoblast into the fetus before or at the time of delivery. This tolerance then persists in adulthood, thereby permitting the successful continuation of pregnancy.

Conversely, one might speculate whether lack of induced tolerance may play a part in the etiology of spontaneous and habitual abortion and the development of congenital defects. The failure to develop tolerance may result in rejection of the pregnancy. This speculatively might then give rise to abortion. Incomplete development of maternal tolerance could conceivably give rise to fetal maldevelopment. If this were a permanent defect it could possibly result in habitual abortion and repeated malformations. The thought arises that it may be possible to prevent such accidents of pregnancy either by some type of desensitization

procedure or by inhibiting a potential antigen-antibody reaction. These latter possibilities are the subject of further investigation.

Summary

1. Syncytiotrophoblast has been demonstrated in 32 of 53 cord bloods obtained at the time of delivery.

2. Decidua-like cells have been found in 14 of 53 cord bloods.

3. Autopsy sections obtained from 25 newborn infants revealed trophoblast in a section of heart and liver.

4. Sections of newborn adrenal gland were found to contain cells in a capillary of the capsule identical with decidual cells.

5. Possible physiologic and immunologic implications of these findings have been discussed.

REFERENCES

1. Schmorl, G.: *Pathologisch-anatomische Untersuchungen über puerperale Eklampsie*, Leipzig, 1893, Vogel.
2. Park, W. W.: *J. Path. & Bact.* 75: 257, 1958.
3. Bardawil, W. A., and Toy, B. L.: *Ann. New York Acad. Sc.* 80: 197, 1959.
4. Douglas, G. W., Thomas, L., Carr, M., Cullen, N. M., and Morris, R.: *AM. J. OBST. & GYNEC.* 78: 960, 1959.
5. Thomas, L., Douglas, G. W., Carr, M. C., and Cullen, N. M.: *Fed. Proc.* 18: 601, 1959.
6. Friedrich, N.: *Virchows Arch.* 36: 465, 1866.
7. Berghinz, G.: *Gaz. Ospedale, Milan.* (Abst. *J. A. M. A.* 34: 1588, 1900.)
8. Priesel, A., and Winkelbauer, A.: *Virchows Arch.* 262: 749, 1926.
9. Weber, F. P., Schwarz, E., and Hellenschmied, R.: *Brit. M. J.* 1: 537, 1930.
10. Holland, E.: *J. Obst. & Gynaec. Brit. Emp.* 56: 529, 1949.
11. MacRae, D. J.: *J. Obst. & Gynaec. Brit. Emp.* 58: 373, 1951.
12. Buckell, E. W. C., and Owen, T. K.: *J. Obst. & Gynaec. Brit. Emp.* 61: 329, 1954.
13. Mercer, R. D., Lammert, A. C., Anderson, R., and Hazard, J. B.: *J. A. M. A.* 166: 482, 1958.
14. Emery, J. L.: *J. Path. & Bact.* 64: 735, 1952.
15. Kay, S., and Reed, W. G.: *Am. J. Path.* 29: 555, 1953.
16. Malmgren, R. A., Pruitt, J. C., Del Vecchio, R. P., and Potter, J. F.: *J. Nat. Cancer Inst.* 20: 1203, 1958.
17. Sandberg, A. A., and Moore, G. E.: *J. Nat. Cancer Inst.* 19: 1, 1957.
18. Billingham, R. E., Brent, L., and Medawar, P. B.: *Ann. New York Acad. Sc.* 59: 409, 1955.

Discussion

DR. LOUIS M. HELLMAN, Brooklyn, New York. This is an astonishing and intriguing paper. Astonishing not that formed elements are shown to pass from mother's circulation to fetal, but that elements the size of syncytial giant cells (100 to 200 μ) cross the barrier in over 50 per cent of the patients tested.

It is now pretty generally accepted from the demonstrations of Nysland with elyptocytes and

Mengert and Macris with sickle cells that maternal red cells find their way into the fetal circulation in a small but definite percentage of cases. The mechanism of this transfer is still far from clear for it would appear to go against the pressure gradient existing between the fetal capillaries and the intervillous space. Page has suggested that such a gradient can be momentarily upset when the mother changes from the

recumbent to the standing position. Also, it is thought that abnormal uterine contractions may reverse the gradient. However, both of these hypotheses require a defect in the integrity of the fetal circulation which if long continued would exsanguinate the baby. The other possible mechanism of such transfer is engulfment of cells by micro villi and transfer to the fetal circulation by the process of pinocytosis. This latter possibility seems to me to be more likely and would certainly more readily explain the transfer of large cellular elements such as trophoblastic giant cells.

These latter are present even very early in gestation scattered on the surface of the syncytial covering of the primitive villi. They extend into the intervillous space and are frequently called "villous sprouts." Undoubtedly some of them develop into future villi. Many, however, never show any development of cytotrophoblast or stroma. Their attachment to the villus becomes more and more attenuated and they finally separate and come to be free in the intervillous space. Neither the cyto- or syncytiotrophoblast nor the "sprouts" ever invade the stroma of the villi in the benign state; however, in moles, especially with increasing malignant change, mesodermal invasion by ectodermal elements is common. This explains the transmission of chorio-carcinoma to the fetus in those rare occasions where there is focal malignancy in an otherwise normal placenta; but invasion cannot explain the transfer of trophoblastic elements from normal placentas. There remains only the traverse from maternal to fetal circulation. If we admit red cell transfer by such traverse, and I believe we do, then there is really nothing against trophoblastic transfer, provided we can be sure of the proper identification of the latter cells.

Dr. Mack and his co-workers assure us that they are well aware of the pitfalls provided by the megakaryocyte in the identification and confusion of trophoblastic elements. They state quite logically that trophoblasts are trophoblasts because they look like trophoblasts. The essayist has demonstrated that the cells seen in the fetal circulation are similar to those taken from a smear of an 8 weeks' placenta. This is good reasoning as far as it goes, although I cannot see why the essayist had to compare 8-week-old trophoblasts in the placenta with term trophoblasts in the cord blood. Nevertheless, the cells in Fig. 3 look like the syncytial elements shown by Douglas in the maternal circulation before this

Society a year ago, and I believe must be taken as such. I find it much harder to agree the cell shown in Fig. 4 is a trophoblastic giant cell. As far as the decidual cells are concerned, I believe these are much harder to identify and that there is really no clear-cut evidence that those seen in the umbilical cord originate from the maternal surface of the uterus.

I am surprised that the authors did not try to pin down the identity of these cells as fetal trophoblast by other means than microscopic similarity. Histochemical staining such as shown by McKay (McKay, D. G., Hertig, A. T., Adams, E. C. and Richardson, M. V.: *Obst. & Gynec.* 12: 1, 1958) would have quite definitely indicated their placental origin. A study of the gradual disappearance of these cells following separation of infant from placenta would have provided further evidence. Final proof that they are fetal although not placental could be obtained from study of their sex chromatin. Unfortunately, this is not technically possible in the case of these giant cells with present techniques, but it could have given undisputable proof of the maternal origin of the decidua-like cells in cases of male babies.

I cannot follow the discussion concerning immunization. While this may be germane as far as the mother goes, the trophoblast is part and parcel of the fetus. It originates from the outer cell membrane covering of the egg and is, I believe, immunologically identical with the fetus. It can no more be antigenic to the infant than can his own blood cells or lanugo.

DR. SALVAGGIO (Closing). We were just as surprised as Dr. Hellman to find this incredible phenomenon because we thought we would find nothing. To our amazement the first specimen studied showed just exactly that, but the second one showed numerous trophoblast cells in the cord blood specimen, and from then on we found them in 65 per cent.

Dr. Hellman asked why we used an 8 weeks' pregnancy to compare the number of cells with those found in the cord blood. We used that for no particular reason other than that the 8 weeks' pregnancy showed distinct clumps of these syncytial trophoblasts. We made a smear in a term pregnancy and demonstrated a very similar type of cell. The others from term pregnancy were also typical.

Dr. Hellman mentioned Fig. 4. This is not

the usual typical trophoblast as we saw it in Fig. 3, but we did not know what else to call it, to be frank. I would like to know if you could give it any other name.

As for stains, we are in the process of using various stains to identify these cells more clearly. The study is not complete as yet. We are also using a fluorescent microscope to get more definite answers about these cells.

Sex chromatin has not been attempted yet and is not likely to be used. As for the decidual cells, we called them decidual-like cells. They are very similar to decidual cells and, until we

can develop a specific stain, we cannot be sure just what they are.

It is interesting that the immunologic significance of this phenomenon was brought out. It is not only true in the fetus but also in the maternal circulation. We are carrying this study on to see if there is any particular immunologic characteristic of pregnancy in an attempt to identify it.

In the pregnancy at 8 weeks in which the trophoblasts were obtained, examination of one section of the fetus revealed a cell very similar to a trophoblastic cell.

CURRENT OPINION

Re-evaluation

Bruit placentaire

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F. I. MAYOR, a Geneva physician, reported for the first time the perception of fetal heart tones¹ and its use in the diagnosis of fetal life. This unique discovery led J. A. Lejumeau de Kergaradec to concentrate on the auscultation of the gravid uterus. Kergaradec was greatly interested in Laennec's stethoscope and was a master with this new instrument. The extensive report of his observations to the Academie Royale de Medecine, Paris, in 1821 included his discovery of a souffle, synchronous with the maternal heartbeat, and he named it "bruit placentaire," or placental souffle.²

The unanimous acceptance of "fetal heart tones" was immediate. The true nature of the bruit placentaire was subsequently questioned. Through the years more observations were reported in which the placental souffle was noted over large myomas and ovarian tumors. It was even described in the postpartum uterus. Depaul³ and Pernice⁴ interpreted the placental souffle to be the result of large vessel compression, explaining its occurrence in large pelvic tumors. Present-day textbooks^{5, 6} still mention the placental

souffle but its origin and significance have been persistently questioned.

Purpose

Previous auscultation over the lower uterine segment in patients with known placenta previa aroused our interest.

This presentation is offered in an attempt to re-evaluate auscultation of the gravid uterus. Particular reference is given to the bruit placentaire as a possible guide in the management of antepartum bleeding.

Material

Forty antepartum patients were selected at random. One of us carried out auscultation of the undelivered uterus and made graphic recordings; the other inspected the uterus immediately after delivery and noted by palpation the exact implantation of the placenta in the uterus. If rapid separation of the placenta in the third stage of labor precluded accurate determination of the placental bed, the patient was eliminated from the series. Patients undergoing cesarean section were included in this study, and the placental site was noted immediately after extraction of the fetus.

Each of us recorded separately all find-

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ings on each patient. These findings were compared at a later date.

Results

Two different sound patterns could be distinguished:

A. Uterine artery sound. A characteristic, harsh, short sound could be heard along the course of the right and left uterine arteries which was synchronous with the maternal heartbeat. This sound was noted in 37 patients (92 per cent). It originated in both lower quadrants and was audible along the uterine borders. It extended frequently up to the level of the superior iliac spines.

Dextrorotation of the uterus changed the otherwise symmetrical position of both arterial sounds. The right uterine artery rotated more posteriorly and its sound was faint or absent. The left uterine artery assumed a more anterior position and could be heard more medially. Observations during labor seemed to indicate that uterine contractions did not alter the intensity of arterial sounds significantly.

B. Placental implantation sound or placental sound (PS). Separate and different in tone quality, this "beehive" sound was observed in 35 patients (87 per cent). It was a continuous, soft, rushing murmur, its intensity varying during maternal systole and diastole. In some individuals the basic sound volume varied so greatly that even relatively loud sounds disappeared altogether for varying lengths of time. This observation necessitated repeated auscultations when the PS could not be located during the initial examination. The PS exhibited a musical component in 13 patients (32 per cent). The uterus remained silent in 5 patients (12 per cent) except for the presence of uterine artery sounds, and in 3 patients (less than 1 per cent) even these arterial sounds could not be heard.

The anatomical proximity of uterine arteries and placenta have, in our opinion, explained intermediate or mixed sound patterns which deserved a meticulous interpretation. Sound quality, quantity, and sound location were the prime factors in the evalu-

ation. The realization that the PS could be lacking its typical characteristics and resemble the sound of uterine arteries was indeed disappointing. Nevertheless, fundal or midline position of such arterial sounds was strongly suggestive of placental origin as it was verified later by manual exploration of the uterus.

The posteriorly implanted placenta was suspected when faint placental implantation sounds were audible near the right and left uterine margin in conjunction with a silent anterior uterine wall.

The prediction of the placental site was exact in 55 per cent and close (within the same uterine segment and within close proximity) in 20 per cent. The location of the placenta was predicted erroneously in 12 per cent.

Comment

The knowledge of the exact location of the placenta is essential in certain complications of pregnancy. The relatively frequent case of vaginal bleeding in the second or third trimester presents a diagnostic problem in which the location of the placenta determines the outcome and the management. Roentgen placentography has as many merits as shortcomings. It becomes a worthless if not dangerous procedure unless taken by expert technicians and evaluated by an experienced radiologist. The palpation of placental tissue through the dilated cervix remains the most valuable clinical test when the placenta is within reach.

The first description of bruit placentaire in 1821 was followed by skepticism. The presence of a souffle synchronous with the maternal heartbeat in the postpartum uterus and over large pelvic tumors was used to disprove its actual existence. Uterine artery sounds may well have accounted for this defeat. The postpartum uterus and the pelvis with extensive tumors are equipped with a pair of hypertrophied uterine arteries capable of producing arterial sounds.

The authors are cognizant of the small number of cases reported in this series. In addition, much was learned after the study

was well under way. It was recognized during this study that two separate sounds, the uterine artery sounds and the placental sound, existed. We became aware that the PS could be completely absent at one time and pronounced later in the same patient. The influence of uterine contractions on the PS sound volume was noted, and contractions produced in some patients a significant decrease in PS volume. The influence of variations of blood pressure on the sound volume has not been studied regularly, but in the occasional patient with transient postural hypotension the sound volume decreased sharply.

It became routine to listen for the placenta in patients with vaginal bleeding in the latter part of pregnancy. The clinical follow-up of these patients proved this physical sign to be of value. A PS heard in the middle or upper third of the uterus in a bleeding patient was useful evidence in excluding placenta previa. On the other hand, a PS heard in the lower segment demanded careful observation. Such a low PS indicated either a low implanted placenta or placenta previa of any degree. Even over large placentas the PS could be confined to only one small area. This precluded exact delineation of placental area.

Six patients included here had placenta

previa. In each instance the PS indicated placental implantation within the lower uterine segment.

Conclusion

The auscultation of 40 antepartum women revealed the existence of two basically different uterine sounds, both synchronous with the maternal heartbeat. Uterine arteries produced a harsh, short, intermittent sound audible along their anatomical course. In contrast with the uterine artery sound, a second sound was noted. It was a soft, continuous "beehive" sound with fluctuations in volume. It was believed to originate from the placenta itself or from the site of placental implantation.

The location of the placenta by auscultation prior to delivery was predicted exactly in 55 per cent, closely in 20 per cent, and erroneously in 12 per cent. The remainder of the patients revealed no placental sound. The implantation was verified by manual exploration of the uterine cavity immediately after delivery of the fetus.

More experience and more observations could lead to a higher degree of clinical usefulness. The bruit placentaire or placental souffle reported more than 100 years ago is, in our opinion, a valuable clinical phenomenon.

REFERENCES

1. Mayor, François Isaac: *Bruit du coeur du foetus*, bibliotheque universelle des sciences, belles lettres et arts, Geneva, 1818, vol. 9, p. 249.
2. Lejumeau de Kergaradec, J. A.: *Memoire sur l'auscultation appliquée à l'étude de la grossesse*, Paris, 1822, Mequignon-Marvis.
3. Depaul, J. A. H.: *Traite theorique et pratique d'auscultation obstetricale*, Paris, 1847, Labe, pp. 167-238.
4. Pernice, Hugo: *Monatschr. Geburtsh. u. Frauenkh.* 15: 179, 1860.
5. Williams, J. W.: *Obstetrics*, ed. 11, New York, 1956, Appleton-Century-Croft, Inc., p. 260.
6. Greenhill, J. P.: *Principles and Practice of Obstetrics*, ed. 10, Philadelphia, 1951, W. B. Saunders Company, pp. 130-132.

Use of the intrauterine stem pessary

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EARLY in 1957 the director of the Food and Drug Administration banned intrauterine stem pessaries from interstate shipment. The precise ruling (dated Jan. 31, 1957) states: "... It is recommended that distributors of these devices remove them from the interstate market at once. Regulatory action may be instituted in connection with any such devices found within the jurisdiction of the act" (Sec. 701, Stat 1055, as amended: 21 U. S. C. 371).

The order was signed by John L. Harvey, deputy commissioner of food and drugs. (We do not know if John L. Harvey also issued the orders concerning cranberries and concerning chickens—eating 500 pounds of either of these foodstuffs at one sitting, it will be recalled, could poison one, not to mention making one feel full.)

The evidence for this ruling did not become available to the profession until some months after the decision was issued. It appeared in the *Western Journal of Surgery, Obstetrics and Gynecology*, Vol. 65, pages 157-160, May-June 1957. The author was Ralph W. Weilerstein, M.D., whose qualifications are unknown to us, except that they do not include certification by the American Board of Obstetrics and Gynecology.

Since the Department of Current Opinion recently (August, 1959, page 446) opened its columns to a very refreshing re-evaluation of the Graefenberg ring without committing itself to advocating a rebirth of the ring, perhaps it could tolerate a re-evaluation of stem pessaries and still retain judicious impartiality.

In 1936 Dr. William H. Weir, now emeritus professor of gynecology at the Western Reserve University School of Medicine, read a paper at the annual meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, reporting his experience with the intrauterine stem pessary in 318 private patients whom he had personally followed and 210 additional cases incompletely followed. In a personal communication he reported that this study and report was prompted by the large number of obstetricians and gynecologists and others who criticized stem pessaries but most of whom had no personal experience with their use and were merely repeating criticisms that they had heard from their teachers or preceptors.

C. Jeff Miller, whose excellent monograph on dysmenorrhea appeared in Curtis' *Obstetrics and Gynecology* in 1935, reviewed the many hypotheses of the cause of dysmenorrhea and also discussed at length the various forms of treatment. He stated that he had personally had very good results from the use of stem pessaries and "had never seen infection follow its use in properly selected cases."

Dr. Weir pointed out that the stem pessary was of "decided value in sterility" and did not cause sterility by producing uterine or tubal infections, as so many of its critics have stated.

One of us (R. W. E.) was formerly a resident in gynecology at the University Hospitals of Cleveland, under Dr. Weir, and had ample opportunity to observe the results

of the use of stem pessaries in both private and service patients. Twenty-four years of experience in private practice and teaching since completion of the residency has strengthened our belief that the intrauterine stem pessary, properly used, is an extremely useful device, not only for the treatment of dysmenorrhea but in sterility and certain types of developmental defects of the pelvic organs. Furthermore, the incidence of complications, particularly infections, is remarkably low.

As the result of the arbitrary decision of the Food and Drug Administration, which we think was not based on adequate and proper information, we determined to review the records of 482 private patients treated with stem pessaries in the 10 year period from Jan. 1, 1947, to Dec. 31, 1956. The results of that study form the basis for this paper.

These cases were divided into three main groups on the basis of the patients' chief complaint at first visit: (1) patients who complained of dysmenorrhea alone (248 cases); (2) patients who complained of sterility alone (126 cases); (3) patients who complained of both dysmenorrhea and sterility (108 cases).

As an indication for advising curettage and stem pessary for dysmenorrhea the patient must have regularly lost time from work or normal occupation and/or have required narcotics for relief.

As an indication for a complete sterility

work-up which often included curettage and stem pessary, the patient must have attempted to become pregnant at least 2 years without success.

In each instance of its use the stem pessary was inserted after curettage under general anesthesia, usually intravenous Pentothal. The stem pessary used was the silver-plated Carsten's type with divergent arms which are held together with an introducer for insertion and which spring apart when released and apply pressure on the cervix at the internal os. A slight enlargement on the end of each arm extends through the internal os to the uterine cavity and holds the pessary in place.

Contrary to the usual belief, these pessaries are not effective contraceptive devices and in at least four instances in the practice of one of us, pregnancy occurred while the patient was wearing a pessary and in each instance the pessaries were removed and the pregnancy proceeded to term. If sterility was a factor at the time of operation, Rubin's test was performed before curettage. If this was negative or equivocal, hysterosalpingogram was done after the stem pessary was removed in most cases. Other laboratory studies such as urinalysis, complete blood count and usually basal metabolic rate or protein-bound iodine determinations were carried out at the time of hospitalization.

The stem pessary was left in place 6 months except in a few instances when the

Table I

Classification of cases	Single				Marital
	Under 20	21-30	31-40	Over 41	
	All nulliparas				Subtotal
Primary dysmenorrhea	41	22	6		69
Secondary dysmenorrhea	16	18	3	1	38
Primary sterility		1			1
Acquired sterility					
P.S.—P.D.					
P.S.—S.D.					
A.S.—P.D.					
A.S.—S.D.					
Total	57	41	9	1	108

stem was partially or completely expelled by the uterus before that time. It was also removed in a very few cases earlier than 6 months because of menorrhagia. One patient developed a pelvic infection after wearing the pessary for 3 months—and the pessary was removed as soon as this was evident. We learned later that the husband had previously had gonorrhea and we suspect that he may have been responsible for the infection. This was the only serious complication in our entire series of cases; the patient made a good recovery after the stem was removed and proper antibiotic therapy given.

We usually employ retroversion pessaries with stem pessaries even though the uterus was originally forward. The stem is often expelled by force of uterine contractions if the uterus is retroverted or in the plane of the vagina. It rarely occurs if the uterus is maintained in a normal anterior position, approximately at right angles to the plane of the vagina.

The patients were seen at intervals of one to 3 months after the initial postoperative visit. A separate file of all patients wearing any kind of pessary is kept and if they do not return for checkup within intervals of 3 months, they are notified by mail or telephone that they should be checked. We have found this an effective way of keeping the patients under strict observation and control.

Most patients have some increase in menstrual flow while wearing the stem and

also an increased mucoid or mucopurulent discharge. A few had uterine cramps—often when not menstruating, especially in the first 4 to 6 weeks of its use. All were instructed to take periodic cleansing douches. All married couples were instructed to resume marital relations after the first post-operative visit.

For purposes of this study we have subdivided the first group into: (A) primary dysmenorrhea which appeared at menarche and (B) secondary dysmenorrhea which appeared (in severe form) later in life.

The second group was divided into two categories: (A) primary sterility—those who had never conceived, and (B) secondary or acquired sterility, those who after having pregnancies were unable to conceive again in 2 or more years during which time contraceptive methods were not used.

The third group, comprising those who complained of both dysmenorrhea and sterility, were subdivided into four categories depending upon the way dysmenorrhea and sterility were related: (A) primary sterility with primary dysmenorrhea (P. S.—P. D.), (B) primary sterility with secondary dysmenorrhea (P. S.—S. D.), (C) acquired sterility with primary dysmenorrhea (A. S.—P. D.), and (D) acquired sterility with secondary dysmenorrhea (A. S.—S. D.).

Patients were also classified as to marital status, age, and parity. The complete data are presented in Table I.

status									Subtotal	Total
Married										
Under 20		21-30		31-40		Over 41				
Nulliparas	Multiparas	Nulliparas	Multiparas	Nulliparas	Multiparas	Nulliparas	Multiparas			
10		53	4	2	5			74	143	
14		29	12	5	6	1		67	105	
2		76		25		1		104	105	
			12		9			21	21	
3		42		5				50	50	
		36		6				42	42	
			4					4	4	
			5		7			12	12	
29	0	236	37	43	27	2	0	374	482	

In general, those complaining of dysmenorrhea alone were younger than those complaining of sterility or dysmenorrhea and sterility. In all categories the greatest number of patients were in the third decade of life.

In the two groups complaining of sterility alone or dysmenorrhea and sterility, a total of 234 patients, 119 had tried for 2 to 4 years

without success; 57 had failed to conceive in 4 to 6 years, and 58 had been unsuccessful after 6 or more years (Table II).

Anteflexions of the uterus and the various types of retrodisplacements were, by far, the most common pelvic findings before operation (Table III).

Other clinical diagnoses made at the first examination are recorded in Table IV.

Table II. Length of sterility prior to first examination

	2 to 3 years	4 to 5 years	Over 6 years
No. cases primary sterility	51	31	23
No. cases acquired sterility	10	8	3
No. cases P.S.—P.D.	30	10	10
No. cases P.S.—S.D.	23	6	13
No. cases A.S.—P.D.	1	1	2
No. cases A.S.—S.D.	4	1	7
Total	119	57	58

Table III. Abnormal positions of the uterus

	Infantile uterus	Anteflexion	Anteflexion-retrocession	Anteflexion-retroversion	Anteflexion-anteversion	Third degree retroversion	Retroflexion	Retroflexion-retroversion	Normal position
Primary sterility	11	60	2	2	1	17	8	2	5
Acquired sterility	0	5	0	0	0	4	7	2	3
Primary dysmenorrhea	9	82	4	3	2	20	10	4	9
Secondary dysmenorrhea	5	43	6	0	2	28	5	5	9
P.S.—P.D.	0	32	1	2	2	3	5	3	1
P.S.—S.D.	2	28	3	2	0	4	1	0	2
A.S.—P.D.	0	2	0	0	0	2	0	0	0
A.S.—S.D.	1	1	2	0	0	5	0	0	0
Total	28	253	18	9	7	83	36	16	32

Table IV. Pelvic findings at first examination

	Sterility		Dysmenorrhea		P.S.—P.D.	P.S.—S.D.	A.S.—P.D.	A.S.—S.D.
	Primary	Acquired	Primary	Secondary				
Ovarian cyst	12	1	4	5	4	3	1	0
Chronic salpingitis	3	1	0	2	1	0	2	0
Chronic cervicitis	15	5	29	13	9	6	3	2
Stenosis of the cervix	2	0	2	4	0	1	0	0
Pelvic adhesions	0	0	0	2	0	0	0	0
Possible endometriosis	13	0	9	5	5	8	0	1
Cervical polyps	0	0	1	0	1	0	0	0

Table V. Operations prior to first examination

	Sterility		Dysmenorrhea		P.S.— P.D.	P.S.— S.D.	A.S.— P.D.	A.S.— S.D.
	Primary	Acquired	Primary	Secondary				
Dilatation and curettage	2	2	5	5	0	0	0	0
Rubin's test	9	2	0	0	0	1	0	0
Hysterosalpingogram	3	0	0	0	0	0	0	0
Unilateral salpingectomy	1	1	0	2	0	0	0	0
Bilateral salpingectomy	0	0	1	0	0	0	0	0
Unilateral oophorectomy	1	0	0	2	1	2	0	0
Unilateral salpingectomy and oophorectomy	0	1	1	0	0	0	0	0
Myomectomy	2	0	0	0	0	0	0	0
Stem pessary	3	0	0	0	0	0	0	0
Total	21	6	7	9	1	3	0	0

Table VI

Type of dysmenorrhea	No. cases	Improvement	Failure
Primary dysmenorrhea	143	142	1
Secondary dysmenorrhea	105	101	4
P.S.—P.D.	50	48	2
P.S.—S.D.	42	41	1
A.S.—P.D.	4	4	0
A.S.—S.D.	12	12	0
Total	356	348	8

Table VII

	Primary sterility	Acquired sterility	P.S.—P.D.	P.S.—S.D.	A.S.—P.D.	A.S.—S.D.	Total
No. of cases	105	21	50	42	4	12	234
<i>Improvement</i>							
Pregnancy	44	4	23	22	3	10	106
Miscarriage	4	0	3	2	1	2	12
<i>Failure</i>							
Husband sterile	19	5	10	4	0	0	38
Husband sub-par	5	1	4	2	0	0	12

Many of the patients in all three major groups had had previous treatment. Medical measures were not recorded as it was difficult to determine what had been done in many instances. Forty-seven of the total group had had some type of surgical treatment previously. These procedures are listed in Table V.

In all, 356 patients complained of dysmenorrhea. Of these, 348 or 98 per cent showed improvement ranging from slight in a few instances only while wearing the pessary, to complete and permanent relief of cramps in most instances. Only eight had no improvement (Table VI). In several instances the patient had complete relief

of the discomfort while wearing the pessary only to have cramps reappear at some time after the pessary was removed. In almost every such case, the recurrent dysmenorrhea was less severe than the original complaint and the patient was grateful for the improvement.

Of a total of 234 patients whose complaint included sterility, 106 became pregnant one or more times after treatment. Of these, 93 produced living children, 11 miscarried before the fifth month (one ectopic pregnancy) and one recently conceived and is now 3 months pregnant. This number was 45.3 per cent of the total, a result that must be considered excellent in view of the fact that of the 129 couples who did not produce a pregnancy, 38 of the husbands were found to be sterile and another 12 were reported of sub-par fertility (Table VII).

We believe there is a definite relationship between dysmenorrhea and sterility in many instances and that the stem pessary is a valuable adjunct in the treatment of both.

Summary and conclusions

1. A total of 482 private patients complaining of dysmenorrhea or sterility, or

both, were treated with intrauterine stem pessaries.

2. Three hundred and fifty-six patients complained of dysmenorrhea. Of these, 348 or 98 per cent showed improvement.

3. Two hundred and thirty-four patients complained of inability to conceive in 2 or more years. Of these, 106 or 45.3 per cent became pregnant one or more times after treatment.

4. Antelexion of the uterus was the most common uterine condition encountered with various types of retrodisplacements of the uterus next in order.

5. The intrauterine stem pessary, usually in combination with a retroversion pessary, is an effective and safe method of treating these conditions.

6. Only one serious complication, acute pelvic inflammatory disease, occurred in this series. There were no deaths.

7. Proper selection of patients with particular emphasis on detecting and eliminating latent pelvic infections is necessary. Adequate control of the patients with periodic checkups must be done to insure satisfactory results with the stem pessary.

Reviews | Abstracts

Edited by

LOUIS M. HELLMAN, M.D.

Selected abstracts

British Medical Journal

Vol. 1, May 7, 1960.

*Gray, J. E.: Rubella in Pregnancy—A Report on Six Embryos, p. 1388.

Gray: Rubella in Pregnancy—A Report on Six Embryos, p. 1388.

The author has meticulously examined the embryos obtained by therapeutic abortion in 6 cases in which rubella occurred between the second and ninth weeks of pregnancy. The embryos measured from 38 mm. crown-rump to 151 mm. In 3 of the 6 cases there were demonstrable abnormalities involving ears, heart, and eyes. In a fourth case there was a possible lesion of the lens and in a fifth case the lens was technically inadequate for examination. It is suggested that the embryo is not capable of responding to infection by means of an inflammatory reaction and must depend upon maternal antibodies; however, a virus which has succeeded in entering a cell is safe from antibodies until the cell dies and the virus is released to be attacked by antibodies. Such scattered cell deaths might produce little evidence in the rapidly growing and multiplying embryonic tissues, but concentrated foci of destruction would appear as simple absence of tissue and of all tissue organized by the destroyed cells. One case of a lesion of Corti's organ demonstrates such theory since the effect would not be noted until the primordium involved embarked upon differentiation at a later date. It is also suggested that the virus may continue to survive intracellularly, especially in the lens, and thus contribute to the unduly high mortality.

Stuart O. Silverberg

*These articles have been abstracted.

May 21, 1960.

*Salm, R., and Simons, P. N.: Intractable Uterine Hemorrhage Due to Abnormal Subendothelial Blood Vessels After Childbirth and Miscarriage, p. 1534.

*Fotherby, K.: Excretion of Pregnanetriol During the Normal Menstrual Cycle, p. 1545.

Salm and Simons: Intractable Uterine Hemorrhage Due to Abnormal Subendothelial Blood Vessels After Childbirth and Miscarriage, p. 1534.

Two cases of severe and intractable menorrhagia in young women are presented which clinically were considered to be functional in origin as no organic cause was clinically demonstrable. Following curettage and even laparotomy in one case, and transfusions totalling 9,600 c.c. in one patient and 7,200 c.c. in the other, without any hematologic or gynecologic cause being found for the severe menorrhagia which would usually start on the second day of the menses, each patient eventually underwent hysterectomy. Pathologic examination revealed the presence of large thick-walled subendometrial blood vessels, which were interpreted as being normal radial myometrial vessels, probably arteries, which had originally supplied the placental site, had increased in caliber during pregnancy but had failed to involute during the puerperium. Erosion of these vessels during menstruation was considered the cause of the exceptionally severe and recurrent menorrhagia.

Stuart O. Silverberg

Fotherby: Excretion of Pregnanetriol During the Normal Menstrual Cycle, p. 1545.

Using recently developed methods of estimating

urinary 5- β pregnane-3 α , 17 α , 20-triol, the author has tried to evaluate any variation in urinary excretion of this steroid during the menstrual cycle and its relation to other steroid excretion patterns. Twenty-four hour urine specimens were collected from 6 normal women for an entire menstrual cycle and the pregnanetriol measured by the manner of Fotherby and Love (1960) and the pregnanediol concomitantly measured. Using Day 0 as the day on which the peak excretion of estrone and estradiol occurred during the follicular phase, the author found that both steroids were excreted in a constant ratio from the last day of menstruation until Day 0, then the pregnanetriol rose at a greater rate than pregnanediol, reaching a level of twice the follicular phase level on Day 3 and remaining elevated until Day 7 when it began to decrease. Pregnanediol, however, began to rise on Day 1 but did not reach its maximum values until Day 7 to Day 9. Thus, pregnanetriol reached a maximum value 2 to 4 days before pregnanediol and began to decrease 2 days before pregnanediol decreased.

The only significance the author is willing to place on the cyclic variation of pregnanetriol excretion is to say that it may have some function other than that of an intermediate in estrogen biosynthesis.

Stuart O. Silverberg

The Canadian Medical Association Journal

Vol. 82, Feb. 6, 1960.

*Rose, V.: Infants of Diabetic Mothers: Clinical and Pathological Features in a Series of 25 Cases, p. 306.

Rose: Infants of Diabetic Mothers, p. 306.

A group of 25 infants of diabetic mothers were observed from birth for the first week of life to determine the clinical and pathological changes occurring in these infants during the early neonatal period.

The maternal history reveals that the parity was high and the incidence of previous stillbirths, miscarriages, and congenital anomalies was significantly higher also. There were 17 patients who had cesarean sections during the thirty-fourth to the thirty-eighth week of gestation. Birth occurred most commonly at 34 to 36 weeks of gestation with the mean weight being 6 pounds, 13 ounces to 7 pounds, 14 ounces. The percentage weight loss during the first 2 days of life was 7.9 per cent (range 1.2 to 14.1).

The prognosis of an infant born to a diabetic mother could not always be foretold by the degree of control of the mother's diabetes. Complications occurred in 11 of the 25 infants and consisted of grunting respirations associated with subcostal indrawing and with cyanosis at times. Some infants seemed to be listless and had an almost shocked appearance, while others were hyperactive with tremors of the limbs and twitching movements.

The concentration of the sugar in the blood of these infants was quite variable but tended to be very low in the first few hours of life. However, these infants never did appear to show signs suggesting clinical hypoglycemia. Electrocardiograms were done on 21 infants and the tracings were variable. Some suggested left ventricular preponderance during the first 48 hours of life and this changed slowly to a normal pattern by the end of the week. The Q-T interval was prolonged in the early tracings and shortened by the end of the week.

The serum potassium level was found to be elevated especially in infants with respiratory distress. The sodium and chloride values were not significantly elevated.

Serum calcium was estimated in 18 infants and found to have a mean of 8.95 mg. per cent \pm 0.92; serum phosphorus a mean of 6.5 mg. per cent \pm 0.61. The mean serum protein level was 5.4 Gm. per cent which is within normal range for newborn premature infants. There could be no correlation between hyperexcitability and hypocalcemia. The excretion of 17-OH corticoids and 17-ketosteroids in the urine of 7 male infants of diabetic mothers and in controls of the same gestational age, showed no significant difference in hormone excretion.

Five infants died within 48 hours of life, and autopsies revealed generalized viceromegaly and immaturity of kidney, liver, and brain tissue. Hyaline membrane formation with atelectasis was present in the lungs of all 5 infants. The pancreas showed islet cell hypertrophy and hyperplasia.

John J. Dettling

Feb. 13, 1960.

*Quinlivan, W. L. G.: Hypofibrinogenaemia Following Normal Pregnancy and Labour, p. 371.

Quinlivan: Hypofibrinogenaemia Following Normal Pregnancy and Labour, p. 371.

The author presents a patient who had a normal

spontaneous delivery after 4½ hours of labor. Following delivery, the patient had a postpartum hemorrhage which did not respond to inspection of the cervix, uterine massage, ergometrine, uterine packing, and blood transfusion. The diagnosis of hypofibrinogenemia was not made until 3 hours after delivery. At this time the level was only 80 mg. per cent, well below the normal range of 200 to 400 mg. per cent. The response to intravenous fibrinogen was instantaneous.

John J. Dettling

April 23, 1960.

*Kelly, H. G., Cross, H. C., Turton, M. R., and Hatcher, J. D.: Renal and Cardiovascular Effects Induced by Intravenous Infusion of Magnesium Sulfate, p. 866.

Kelly et al.: Renal and Cardiovascular Effects Induced by Intravenous Infusion of Magnesium Sulfate, p. 866.

This paper reports the effect of intravenous infusion of magnesium sulfate on blood pressure and renal function in both hypertensive and normotensive subjects.

When the dose was large enough it brought about a feeling of warmth and flushing, a fall in blood pressure, and increased renal blood flow, all of which indicate generalized vasodilatation. The fall in blood pressure was more easily obtained and was more marked in hypertensive subjects.

Renal plasma flow was increased and was accompanied by an increased glomerular filtration rate in hypertensive but not in normal subjects.

The rise in plasma magnesium level was accompanied by a fall in plasma calcium but no change in other electrolytes. Larger amounts of calcium and magnesium were excreted by the normal than by the hypertensive kidney. Sodium and chloride were also excreted in larger amounts by the normal kidney. The hypertensive kidney excretes more potassium; the normotensive kidney less. No consistent change in phosphorus excretion was noted. The water diuresis during the infusion was greater in normals.

The significance of these changes is discussed.

John J. Dettling

German Medical Monthly

Vol. 5, March, 1960.

*Rimbach, E., and Bonow, A.: Changes in Transaminase Activity During Pregnancy and the Puerperium, p. 85.

*de Ruder, B.: The Growing Incidence of Severe Congenital Abnormalities, p. 85.

Rimbach and Bonow: Changes in Transaminase Activity During Pregnancy and Puerperium, p. 85.

Studies of serum levels of glutamic-oxalacetic transaminase (SGOT) and glutamic-pyruvic transaminase (SGPT) were undertaken during pregnancy. No appreciable difference was noted in SGOT or SGPT values among 25 healthy nonpregnant and 25 normal pregnant women. SGOT and SGPT values roughly doubled toward the end of parturition, falling steadily to normal by the fourth to the tenth day. Hemorrhage from placenta previa was accompanied by a rise of enzyme activity. Transient increases in SGOT activity were observed in 2 patients following cesarean section for contracted pelvis, while SGPT remained normal. No alterations were noted during the puerperium or during involution of the uterus. The authors attribute the increased enzyme activity in placenta previa and during delivery to an increased permeability of the placenta, allowing enzymes to enter the maternal circulation.

Edward E. Wallach

de Ruder: Growing Incidence of Severe Congenital Abnormalities, p. 85.

The experience with severe congenital deformities of the vertebral column at the University Children's Clinic at Frankfurt is cited. Since 1951 the number of cases of meningocele, myelocoele, and meningomyelocoele has increased sevenfold over prewar admissions, the incidence per thousand infants has increased from 1.87 (1936 to 1939) to 6.41 (since 1951). No etiological factors are suggested, and an attempt has been made to rule out external factors.

Edward E. Wallach

Irish Journal of Medical Science

No. 412, April, 1960.

*Delaney, E. J.: Pelvic Floor Repair Under Lumbar Epidural Analgesia and Promazine (Sparine), p. 187.

Delaney: Pelvic Floor Repair Under Lumbar Epidural Analgesia and Promazine (Sparine), p. 187.

The technique of lumbar epidural analgesia as used in 50 cases of pelvic floor repair is described in detail. The main features of the technique are that the patient is put in the left lateral position. Injection is made anywhere be-

tween T-12 and S-1 but the most suitable is generally found to be between L-3 and L-4. As the dura is not punctured there is no risk of damaging the cord. When the ligamentum flavum is pierced and the extradural space is entered 20 to 30 c.c. of 1.5 per cent Lignocaine-Adrenaline solution is injected. After 15 to 20 minutes the blood pressure falls to about 80 mm. The patient is then placed in the lithotomy position and the operation commenced. If the blood pressure tends to fall below 100 mm. Hg small doses of norepinephrine are injected. Severe falls in blood pressure occasionally occur but these can be reversed quickly by careful watch of blood pressure and immediate use of norepinephrine intravenously. Total spinal block due to injection of a large quantity of local anesthetic into the subarachnoid space is a complication which must be kept in mind. If there is an awareness of the complication, it does not constitute a risk to the patient and cannot be used as an argument against extradural analgesia. The author states that lumbar epidural block is the most satisfactory form of local analgesia for pelvic floor repair. He does not mention the advantage, if any, over caudal analgesia but states that it is no more difficult to administer than a spinal block. Promazine (Sparine) seems to have as good a tranquilizing effect as chlorpromazine (Largactil) without the serious falls in blood pressure sometimes seen with this drug.

Edward Solomons

The Journal of Clinical Endocrinology and Metabolism

Vol. 20, February, 1960.

*Van Wyk, J. J., Dugger, G. S., Newsome, J. F., and Thomas, P. Z.: Effect of Pituitary Stalk Section on Adrenal Function of Women With Breast Cancer, p. 157.

*Lipsett, M. B., and Riter, B.: Urinary Ketosteroids and Pregnanetriol in Hirsutism, p. 180.

Van Wyk et al.: Effect of Pituitary Stalk Section on Adrenal Function of Women With Breast Cancer, p. 157.

Pituitary stalk section was performed in 26 women with rapidly advancing carcinoma of the breast. A tantalum plate was inserted above the sella to retard revascularization from the hypothalamus. Summarized results of detailed studies of adrenal function both before and after the

operations are given. Many of the patients excreted low or low-normal quantities of 17-ketosteroids and 17-hydroxycorticosteroids prior to operation. Following the operation, steroid excretion gradually decreased to the low levels observed in hypopituitarism and characteristic symptoms of adrenal insufficiency developed. These symptoms were alleviated by the administration of ACTH prednisolone. When substitution therapy was withheld, there was no tendency for urinary steroids to rise and symptoms of adrenal insufficiency recurred. The capacity of the pituitary-adrenal axis to respond to "stress" was assessed by measurement of the rise in the concentration of plasma 17-hydroxycorticosteroids during an insulin-glucose tolerance test and after the administration of bacterial pyrogen. The response was compared with the response to ACTH. The postoperative response to ACTH was frequently diminished or absent, suggesting that varying degrees of adrenal atrophy had occurred. The response to hypoglycemia of pyrogen, however, was usually as great as that obtained by ACTH.

J. Edward Hall

Lipsett and Riter: Urinary Ketosteroids and Pregnanetriol in Hirsutism, p. 180.

The urinary excretion of 17-ketosteroids and pregnanetriol was compared in a group of normal young women and in a group of 11 women whose presenting complaint was hirsutism.

Androsterone, etiocholanolone, dehydroepiandrosterone, 11-hydroxyetiocholanolone, 11-ketiocholanolone, and 11-hydroxyandrosterone were determined quantitatively by paper chromatography. Among the hirsute women an elevated excretion of androsterone and etiocholanolone was noted in 6 and of dehydroepiandrosterone in 5. The 11-oxyketosteroids tended to be higher in the hirsute group although no statistical significance was attained. Pregnanetriol excretion was normal.

Hirsutism may be associated with elevated excretion of 11-deoxyketosteroids, but it is impossible to predict clinically which patients will fall into this group. There is little overlap clinically between hirsute women and virilized women. This suggests a qualitative difference in androgen production. The significance of the association of elevated excretion of androgen metabolites and hirsutism remains to be determined.

J. Edward Hall

March, 1960.

*Ronan, F. F., Parsons' L., Namiot, R., and Wotiz, H. H.: Excretion of Pregnanetriol During Pregnancy, p. 355.

Ronan et al.: Excretion of Pregnanetriol During Pregnancy, p. 355.

Evidence is presented that certain enzyme preparations are unable to hydrolyze pregnane-3 α , 17 α and 20 α -triol, although they readily cleave pregnane-3 α , 20 α , diol. Comparison of enzymatic hydrolysis with mineral acid hydrolysis showed that the latter caused conversion of pregnanetriol to a substance with chromatographic properties similar to those of pregnanediol, resulting in interference with the assay of pregnanediol. The excretion of pregnanetriol during pregnancy (7 cases studied) showed two major peaks in the first and third trimesters. Between these peaks there was complete disappearance of pregnanetriol from the urine at about the twelfth week. This suggests that the site of production of pregnanetriol precursors had shifted from the ovary and possibly the adrenal cortex to the placenta.

J. Edward Hall

April, 1960.

*Mills, I. H., Scheol, H. P., Chen, P. S., Jr., and Bartter, F. C.: Effect of Estrogen Administration on Metabolism and Protein Binding of Hydrocortisone, p. 515.

*Assali, N. S., Dignam, W. J., and Long, L.: Renal Function in Human Pregnancy. III. Effects of ADH on Renal Hemodynamics and Water and Electrolyte Excretion Near Term and Postpartum, p. 581.

Mills et al.: Effect of Estrogen Administration on Metabolism and Protein Binding of Hydrocortisone, p. 515.

A study was made of the effect of estrogen administration on the plasma hydrocortisone level in normal subjects with and without concomitant cortisone therapy. Plasma hydrocortisone levels in some instances fall progressively during the control period with cortisone alone. This is reversed by ultrafiltration at 37° C. and double isotope tracer techniques, the protein-bound and nonprotein-bound fractions of plasma hydrocortisone were studied. Approximately 5 to 10 per cent was not protein bound. This percentage was reduced, but absolute values remained the same, when estrogen was given. The rise in the plasma level of hydrocortisone rep-

resented an increase in the protein-bound fraction, and in vitro techniques revealed an increase in the binding protein or in the number of sites. The increased plasma levels due to estrogen therapy were not associated with depression of eosinophils, which suggests that only the non-protein-bound fraction is biologically active. The half-time for disappearance of plasma hydrocortisone is considerably prolonged by administration of estrogen, this probably represents protection from destruction by the liver by means of greater protein binding. The effects of estrogen in altering hydrocortisone metabolism are comparable to those produced by pregnancy.

J. Edward Hall

Assali, Dignam, and Long: Renal Function in Human Pregnancy, p. 581.

It has been suggested that pregnant women are less sensitive to the action of ADH because they possess an inactivating mechanism for this hormone. This hypothesis was tested by studying the effects of intravenous administration of Pitressin on renal hemodynamics and water and electrolyte excretion in pregnant women in the latter part of gestation and in postpartum and nonpregnant subjects. During pregnancy, a single intravenous dose of 100 mU. of Pitressin or continuous infusion of this hormone in doses varying from 25 to 100 mU. per hour produced a marked fall in urine flow with a simultaneous fall in renal plasma flow, glomerular filtration rate, and the output of sodium, chloride, and total solute. Potassium excretion was inconsistent. Osmolal and free water clearance fell, the latter becoming negative in most instances. Following delivery or in the nonpregnant state, the same or higher doses of Pitressin produced a reduction in urine flow which was of the same magnitude and pattern as that in the pregnant subjects. However, renal hemodynamics remained unchanged and electrolyte excretion even increased. This response was typical of the action of Pitressin as described in the literature. Although various hypotheses are offered to explain the altered response to Pitressin in pregnancy, at present it is not possible to identify precisely the factors that account for the change in renal hemodynamics and the fall in solute excretion. The results of the present study do not lend support to the hypothesis suggested by others that an inactivating mechanism for ADH exists in human pregnancy.

J. Edward Hall

Journal of Reproduction and Fertility†*Vol. 1, February, 1960.*

Lindahl, P. E.: Some Factors Influencing the Biological Activity of Sperm Antagglutins, p. 3.

Hartree, E. F., and Mann, T.: Phospholipids in Mammalian Semen, p. 23.

Lake, P. E.: Studies on the Dilution and Storage of Fowl Semen, p. 30.

Adams, C. E.: Prenatal Mortality in the Rabbit, *Oryctolagus cuniculus*, p. 36.

*Scott, L. Stuart: Varicocele Ligation with Improved Fertility, p. 45.

Beatty, R. A.: Fertility of Mixed Semen from Different Rabbits, p. 52.

*Short, R. V.: Blood Progesterone Levels in Relation to Parturition, p. 61.

Perry, J. S.: The Incidence of Embryonic Mortality as Characteristic of the Individual Sow, p. 71.

*Harvey, Clare: The Speed of Human Spermatozoa and the Effect on It of Various Diluents, With Some Preliminary Observations on Clinical Material, p. 84.

Bruce, H. M.: A Block to Pregnancy in the Mouse Caused by Proximity of Strange Males, p. 96.

Proceedings of the Society for the Study of Fertility: Annual Conference, Dublin, 1959, p. 104.

Scott: Varicocele Ligation With Improved Fertility, p. 45.

A study was made of 55 consecutive cases in which the author carried out high ligations of different sizes of varicocele and compared the results to 4 subfertile men who had no varicocele but voluntarily submitted themselves to the identical operative procedure. Seminal specimens were analyzed before and after operation and a count of 20 million per cubic centimeter or above with 50 per cent motility after 4 hours was considered normal. The operative technique was simple and ligation and division of the vessel was carried out just below the deep inguinal ring. A low grade motility associated with an adequate sperm count was one of the strongest indications for varicocele ligation. The

results were good. A return to fertile levels in the semen occurred within 6 months of operation in approximately 3 out of every 4 cases although there was an initial postoperative depression of the sperm count. Complete necro-spermia associated with a normal sperm count showed an excellent response in 75 per cent of the cases. A significant increase in the pregnancy rate followed within a few months of operation.

Alvin M. Siegler

Short: Blood Progesterone Levels in Relation to Parturition, p. 61.

The hormonal mechanism that initiates parturition is still not clearly understood although numerous theories have been used to explain it. The author reviews some of the evidence for and against the importance of oxytocin, estrogen, and progesterone. He studied in detail the blood progesterone levels in the peripheral blood of women, horses, cattle, sheep, and pigs with his assay technique. He concludes that parturition is not under the control of a single hormonal factor and, in fact, there is no evidence to suggest that progesterone is involved in parturition in man.

Alvin M. Siegler

Harvey: Speed of Human Spermatozoa and Effect on It of Various Diluents, p. 84.

A method is described for the measurement of the speed of human spermatozoa. As the selected sperm crosses a line of grid the stop watch is started. As the sperm passes from square to square the direction of movement is spoken into the microphone. The track is followed for 5 to 10 squares of a counting chamber and as the last line is crossed the watch is stopped. The time for recording 20 tracks varies from 3 to 5 minutes so that observations are completed 7 minutes after semen and diluents are mixed, and tests in different suspensions can follow one another at 1½ minute intervals. Dilution with seminal plasma, buffered glucose solution, and normal saline cause a fall in the average velocity of spermatozoa. Seminal plasma from other semen samples may have a stimulating or a depressing effect on speed when added to semen but in most cases produces no change. The speed of spermatozoa in cervical mucus as in semen indicates that it would be possible for them to enter the Fallopian tubes by their own activity within 30 minutes after insemination.

Alvin M. Siegler

†A welcome addition to the list of scientific periodicals is the *Journal of Reproduction and Fertility*. The publication is to replace the published proceedings of the Annual Conference of the British Society for the Study of Fertility, and it will include relevant papers on scientifically based animal and human studies which bear on the urgent problem of fertility.

Alvin M. Siegler

Lancet

Vol. 1, Feb. 20, 1960.

***Arge, E.:** Transposition of the Viscera and Sterility in Men, p. 412.

Arge: Transposition of the Viscera and Sterility in Men, p. 412.

Four instances of complete visceral transposition (3 male and 1 female) among 2 sibships were studied. All of these individuals were double first cousins and furthermore all had common great great grandparents. The family tree showed 9 siblings in each sibship. All who married have children except the men with visceral transposition. The woman with visceral transposition has had one child. Because 2 of the men and their wives were over 50 years of age they refused examination. The third man was young enough to want children and his wife had had 2 children by a previous marriage. Examination of the seminal fluid from this man showed that 91 per cent of the spermatozoa were immobile and the survival time was less than 24 hours. Abnormal head shapes were found in 47 per cent of the 9.5 million spermatozoa per milliliter ejaculum.

The genitals appeared to be normal. Biopsy showed slight degenerative damages and brisk, somewhat abnormal spermatogenesis.

Although confirmation was thought to be necessary, the possibility that men with transposition of the viscera may be infertile or subfertile was considered.

David M. Kydd

April 2, 1960.

***Corner, Beryl, Berry, Elizabeth, and Neale, A. V.:** Hyperbilirubinemia in Premature Infants and the Effect of Synthetic Vitamin K, p. 715.

***Polani, P. E., Briggs, J. H., Ford, C. E., and Clarke, C. M.:** A Mongol Girl With 46 Chromosomes, p. 721.

***Fraccaro, M., Kaijser, K., and Lindsten, J.:** Chromosomal Abnormalities in Father and Mongol Child, p. 724.

Corner, Berry, and Neale: Hyperbilirubinemia in Premature Infants and Effect of Synthetic Vitamin K, p. 715.

In Bristol from 1948 to 1954 kernicterus without evidence of hemolytic disease was found post mortem in 67 of a total of 2,599 premature infants (2.6 per cent). This agreed with the incidence of 2.3 per cent reported from Birmingham but was quite different from the fact that

during the same period only 3 such patients were found at the Boston Lying-in Hospital. During that period it was the practice in Bristol to administer to all babies the synthetic analogue of Vitamin K, tetrasodium 2-methylnaphthalene-1:4-diol phosphate (Synkayvit). During the next year when a study was undertaken to explain the difference in incidence in Bristol from that in Boston no patients with kernicterus without isoimmunization were found and it was found that unknown to the investigators another analogue of Vitamin K, menaphthone dipotassium sulphate, or Vikastab, had been substituted for Synkayvit. At that time reports appeared (Allison, A. C.: *Lancet* 1: 669, 1955; Bound, J. P., and Telfor, T. P.: *Lancet* 1: 720, 1956) associating the administration of Synkayvit with elevated serum bilirubin levels. Consequently this study tests the effect of the analogue Vikastab upon the serum bilirubin level.

Of 436 patients 107 received no drug, 94 received 5 mg., 138 received 10 to 15 mg., and 97 between 30 and 60 mg. of the drug. The infants were also divided into groups according to gestational age. Over-all there was no statistical difference in the maximal serum bilirubin values obtained whether or not the infants received the synthetic Vitamin K analogue. Unlike Synkayvit menaphthone dipotassium sulphate Vikastab did not influence the development of hyperbilirubinemia in premature infants.

A definite correlation between the average maximum serum bilirubin values and the age of gestation was found so that the conclusion is reached that hyperbilirubinemia in premature babies is primarily related to immaturity and is not affected by this particular synthetic Vitamin K analogue.

David M. Kydd

Polani et al.: A Mongol Girl With 46 Chromosomes, p. 721.

In the 30 instances of Mongolism that have been reported so far analysis of the cells has shown 47 chromosomes and the individuals are trisomic for one of the two short pairs of acrocentric chromosomes. Most patients whose chromosomes have been studied and reported upon probably were the offspring of older mothers.

Three Mongoloid children were selected because they were born from young mothers and had no family concentration of Mongolism. Cells from the bone marrow were cultured and

analyzed. Of these 3 marrow cultures one failed and another yielded a chromosome count of 47 similar to those that have been previously reported. The third culture showed cells containing 46 chromosomes. This latter was obtained from a girl of 10; diagnosis of Mongolism had been made neonatally. The mother had been repeatedly treated by x-ray because of inactive pulmonary tuberculosis. She was 21 years of age when the Mongoloid child was born. Three years later she gave birth to a normal male. The father was 23 years of age and healthy. The preparation was analyzed by 2 observers, both of whom found 46 chromosomes. On detailed analysis of 15 cells only 4 short acrocentric chromosomes as in normal females were found. Of the group of 6 chromosomes of pairs 14, 15, and 16 normally present, 5 were found but there were 17 medium length chromosomes instead of 16 as in a normal female. The "extra" chromosome could not readily be distinguished from the 2 members of pair 12. However, although the possibility of trisomy of chromosome 12 together with a monosomatic condition of chromosome (?)15 could not be excluded. The hypothetical combination in one viable individual of a monosomatic condition and of Mongolism originating through a chromosomal mechanical (trisomy of pair 12 rather than 22) entirely different from the one that has been demonstrated hitherto seemed to be highly unlikely. The supposition was made therefore that the "extra" chromosome was compounded of the greater part of the missing one of pair (?)15 and the expected additional chromosome 22. The most likely interpretation was an unequal reciprocal translocation between chromosomes (?)15 and 22 with both points of exchange close to the centromere.

Five possible origins of this defect were considered, 2 somatic, 2 germinal, and 1 both somatic and germinal: (1) during embryogenesis from a zygote with 46 chromosomes or even locally in the bone marrow after embryogeny was complete; (2) during embryogenesis from a zygote with the 47 chromosomes usual in Mongolism or later locally in the bone marrow; (3) during gametogenesis in one of the parents; (4) during embryogenesis in one of the parents with consequent involvement of all or part of one or both gonads; (5) during embryogenesis of one of the 4 grandparents. Although neither can be rigorously excluded, possibilities 1 and 2 appear unlikely, for if the first cleavage divi-

sion is excluded both would lead to chromosomal mosaicism (i.e., 2 types of cells differing in chromosomal constitution), of which there was no evidence in this patient. Any of the other 3 possibilities appeared to be more likely if the possibility that a different mechanism for Mongolism may be a specific chance happening is not considered to be likely.

This is the second instance of presumptive translocation that has been reported. The other was in a patient with polydyspondylie whose dividing cells contained only 45 chromosomes (Turpin, R.: *Int. Pediat. Cong.*, 1959; Lejenne, J.: *Conference on Human Chromosome Abnormalities*, Kings College Hospital, London, 1959).

David M. Kydd

Fraccaro, Kaijser, and Lindsten: Chromosomal Abnormalities in Father and Mongol Child, p. 724.

The patient who was recognized soon after birth as being a Mongol was born in 1959. His mother, aged 37, had had 4 previously normal pregnancies and gave no history of irradiation of the pelvic region. The father, aged 58, was in good health. Cells obtained from the skin and bone marrow of the infant, from the skin of the father, and from the bone marrow of the mother were cultured by the technique of Fraccaro, Kaijser, and Lindsten (*Ann. Human Genet.* 24: 45, 1960). Cells from the infant contained 46 chromosomes, from the father 47 chromosomes, and from the mother 46 chromosomes. Analysis of the cells from the mother indicated a normal female karyotype. Analysis of the cells from the father showed that the forty-seventh chromosome was small with a submedian centromere. It was tentatively concluded that the father was trisomatic for chromosome 19 (in this classification the chromosome present in triplicate in Mongolism is 21). Analysis of the cells from the infant showed only 4 short acrocentric chromosomes, one of which was easily identified as the Y chromosome. Five chromosomes in the small size range with submedian centromere were found instead of the 4 normally present. The interpretation was made that the "fifth" chromosome was either the product of a reciprocal translocation between 2 of the triplicated No. 21 chromosomes or a triplicate of No. 19.

Two hypotheses were discussed: (1) the infant inherited two No. 19 chromosomes from

his father and one from his mother (trisomic No. 19). In this case he must have been monosomatic for pair No. 21; (2) the infant inherited only one No. 19 chromosome from his father and one from his mother, and the "fifth" chromosome was produced by a reciprocal translocation between two No. 21 chromosomes. In both cases an abnormality of chromosome No. 21 occurred. In (1) the infant was both trisomic and monosomatic for two different autosomes, which is unlikely but has been reported (Böök, J. A.: Acta soc. med. uppsala. In press). If hypothesis (2) be correct reciprocal translocation may occur between homologous chromosomes. In (1) the defect in the infant might be explained by the assumption that genes in the single No. 21 chromosome manifest themselves since they are in a hemizygous state. In (2) the greater part of three No. 21 chromosomes are present—a sufficient condition for the phenotypical presence of Mongolism.

Until the normal siblings of the affected infant are examined to learn whether any are trisomic for No. 19 chromosome, either hypothesis may be correct.

If the father is truly trisomic and not a mosaic of normal and trisomic cells the conclusion was made that trisomy does not necessarily involve pathological manifestations possibly because one of the two chromosomes is genetically inert as are generally the supernumerary

chromosomes found in some plant and invertebrate species.

David M. Kydd

April 16, 1960.

*Böök, J. A., and Santesson, Berta: Malformation Syndrome in Man Associated With Triploidy (69 Chromosomes), p. 858.

Böök and Santesson: Malformation Syndrome in Man Associated With Triploidy (69 Chromosomes), p. 858.

In this preliminary report the first known instance of triploidy in the human species is reported. The patient, a male 11 months of age, had numerous defects (disturbances of consciousness, deficient intellectual contact, localized lipomatosis, micrognathia, cutaneous and bony syndactyly). Neither his parents (aged 30 and 29 years) nor an older brother had evidence of any defect. X-ray examination showed 9 bone nuclei rather than the expected 16, and pneumoencephalogram showed porencephaly.

Cells obtained from the skin were cultured and analysis showed that all acceptable metaphases contained 69 chromosomes. Occasional cells with lower or higher numbers were seen. These studies indicated the presence of 3 haploid sets, i.e., chromosome complement of 3A + XXY.

David M. Kydd

Item

**American Board of Obstetrics
and Gynecology**

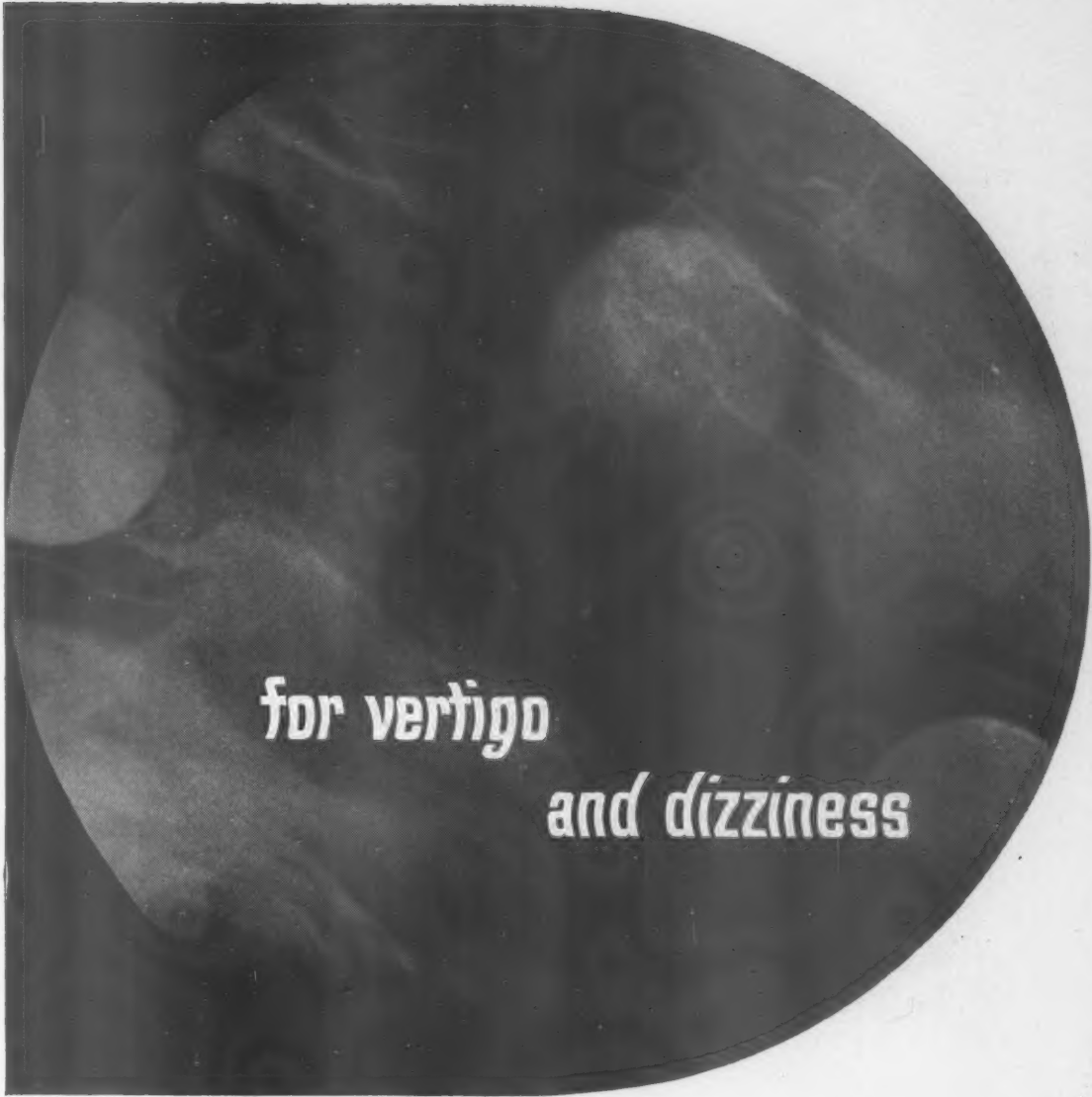
The Part I Examinations (Written) will be held in various cities of the United States, Canada, and military centers outside the Continental United States on Friday, Jan. 13, 1961.

Reopened candidates will be required to submit Case Reports for review 30 days after notification of eligibility. No reopened candidate

may take the Written Examination unless the case abstracts have been received in the office of the Executive Secretary.

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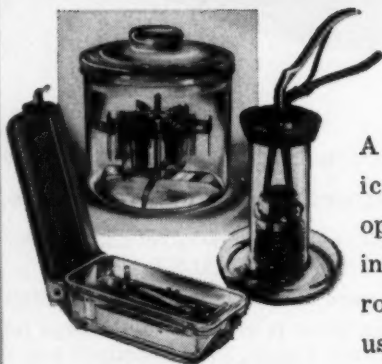
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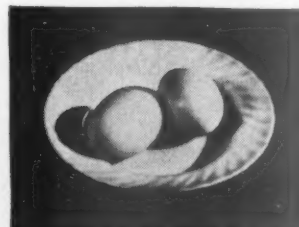
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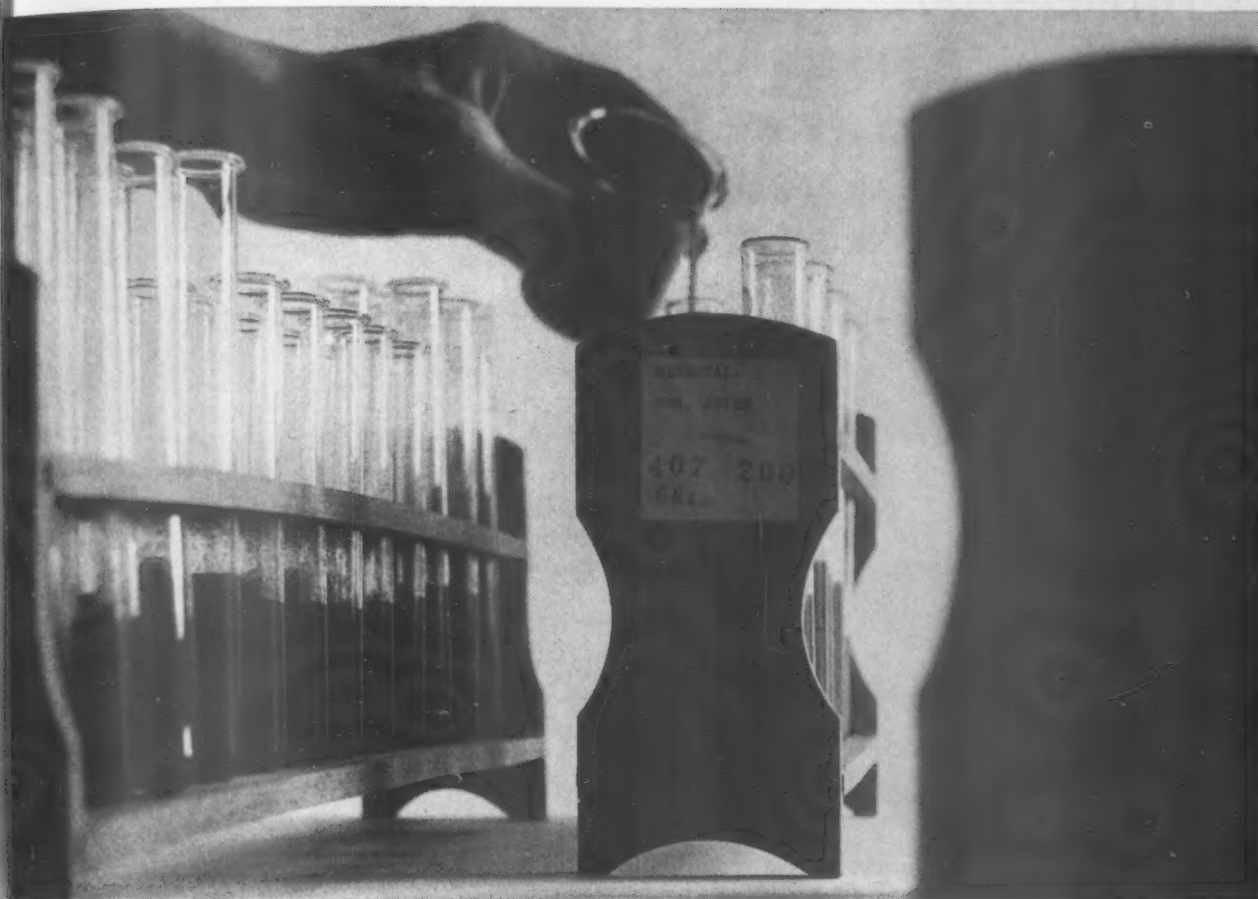
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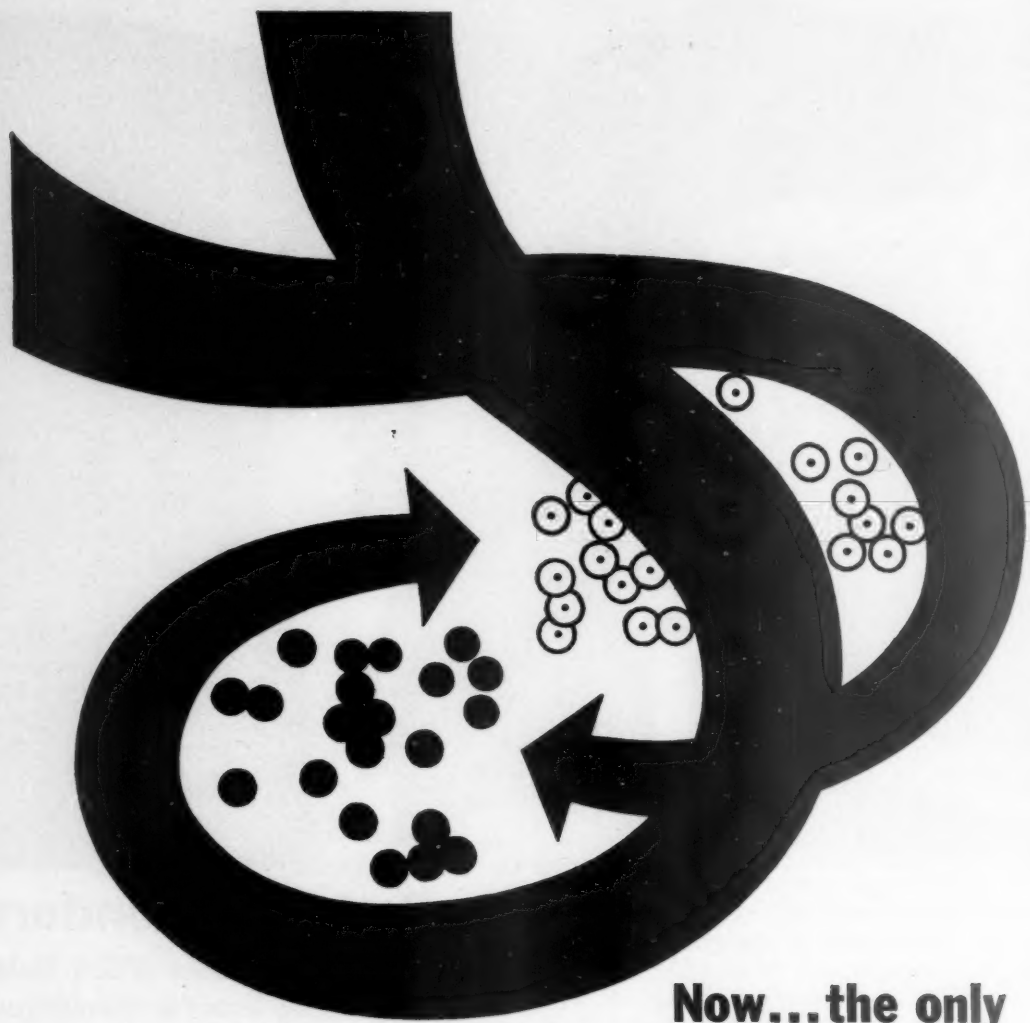


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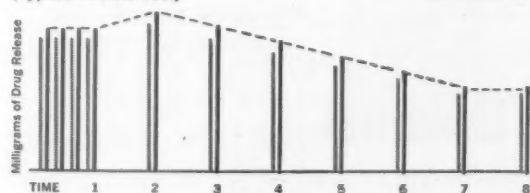
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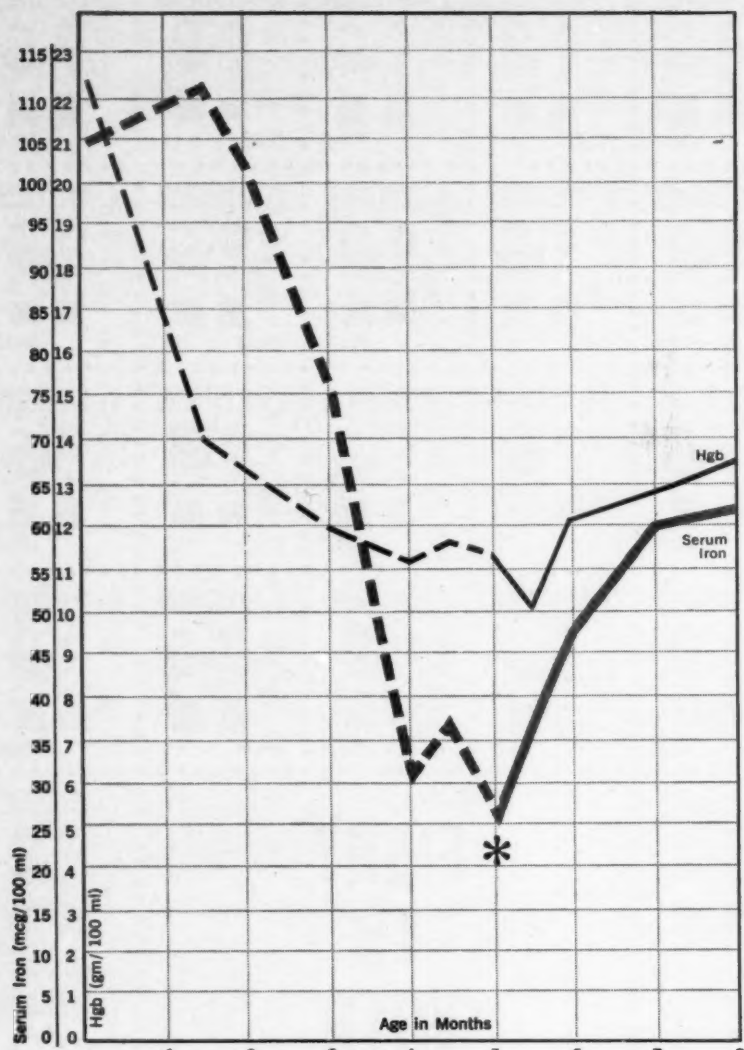
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1. Marsh, A. K.: Personal communication.
2. Lahey, M. E.: *Pediat. Clin. North America* 4:481 (May) 1957.

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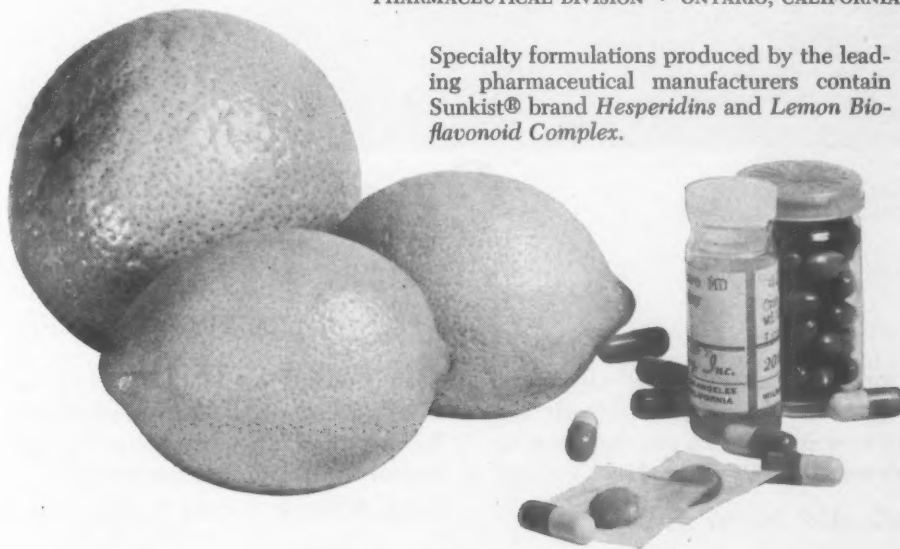
The rationale of Hesperidin and other citrus bioflavonoids — in conjunction with vitamin C, nutritional factors and other therapeutic measures — as adjuncts, is based on the premise that capillary involvement may be a contributing factor in spontaneous abortion and erythroblastosis fetalis.

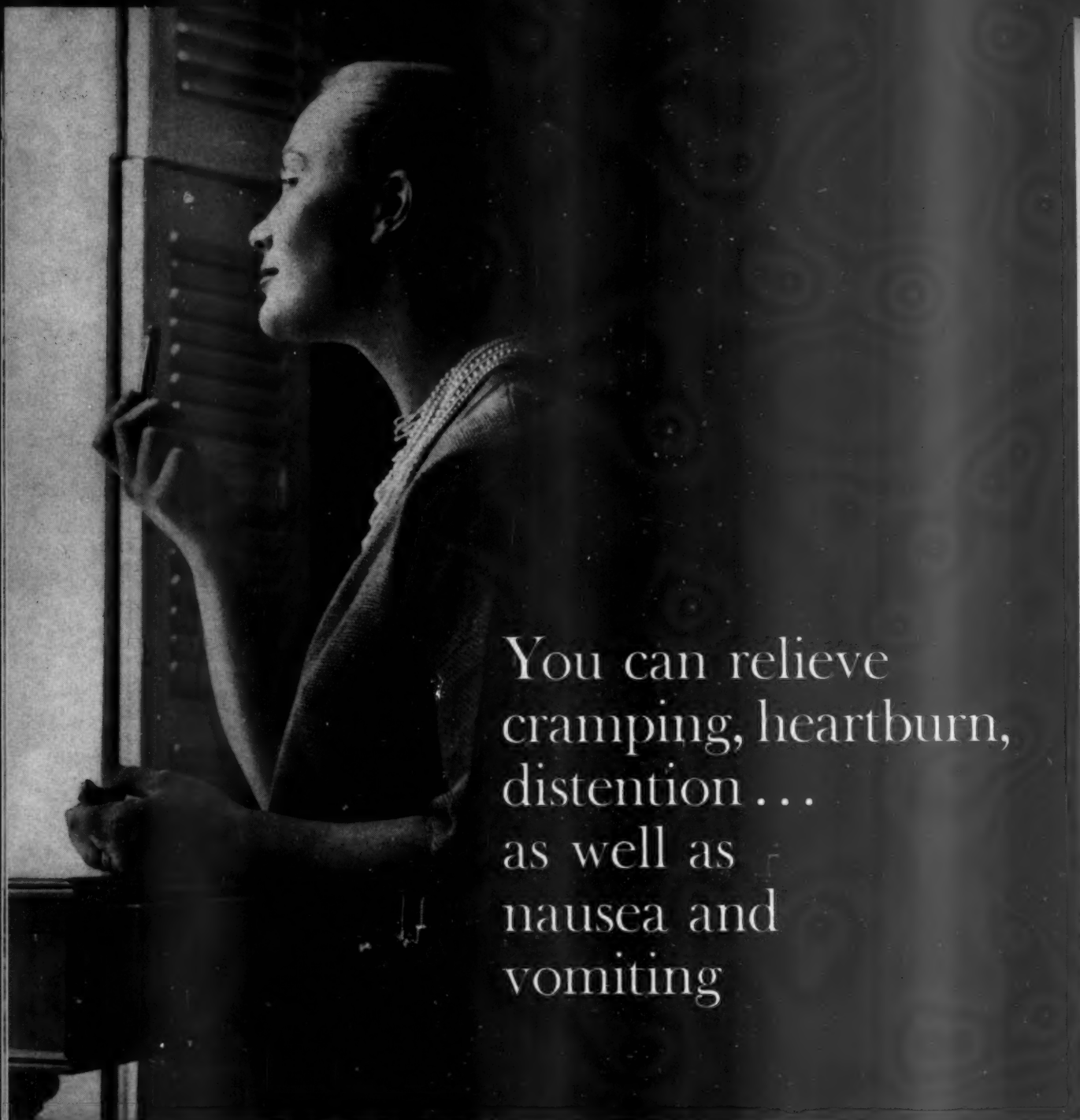
Hesperidin, Lemon Bioflavonoid Complex and their naturally occurring synergist ascorbic acid are readily available capillary protective factors for the restoration and maintenance of capillary integrity and function.

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as well as
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Zinc Bacitracin	500 Units	400 Units	400 Units
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Hydrocortisone	—	—	10 mg.
Supplied:	Tubes of 1 oz., ½ oz. and ⅛ oz. (with ophthalmic tip)	Tubes of 1 oz., ½ oz. and ⅛ oz. (with ophthalmic tip)	Tubes of ½ oz. and ⅛ oz. (with ophthalmic tip)



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orien in der Chirurgie, Med. Klin. 49:1921-22, 1954. 53. Millack, J.: Obstipationstherapie während der Gravidität
raxis 9/6: (Feb.) 1957. 54. Moreton, R. D.: The roentgenologic examination of the colon, presented at the Annua
of the American Roentgen Ray Soc., Wash., D.C., Oct. 1, 1958. 55. Ohling, A. C.: Rektale Anwendung von Laxantien
ische 22:819-821, 1955. 56. Pincock, J. G.: The use of a rectal suppository of bisacodyl (Dulcolax) in geriatric patients
M.A.J. 82:268-269 (Jan. 30) 1960. 57. Poppel, M. H.: Bowel preparation for radiologic procedures using a new evacuant
1, Am. J. Roentgenol. 81:696-699 (Apr.) 1959. 58. Raskin, H. F., Palmer, W. L., and Kirsner, J. B.: Exfoliative cytology
osis of cancer of the colon, Dis. Colon & Rectum 2:46-57 (Jan.-Feb.) 1959. 59. Raymond, O.; Nogrady, B., and Vézina
ffective evacuation of the colon by a new therapeutic agent proven in radiology, Scien. Exhibit presented at the 22nd
Meeting of the Canadian Assoc. of Radiologists, Saskatoon, Sask., Canada. 60. Raymond, O.; Nogrady, B., and Vézina
ffective evacuation of the colon by a new therapeutic agent (bisacodyl) proven in radiology, Canad. M.A.J. 82:1077-80
) 1960. 61. Roth, F.: Dulcolax als Klyisma-Ersatz in der Geburtshilfe und Frauenheilkunde, Ther. Umschau, Bern 15:55-58
1958. 62. Rutter, A. G.: Bisacodyl; an evacuant drug, Lancet 708:111-113 (June 6) 1959. 63. Sánchez Capelot, Francisco
chez Martin, Agustín: Experimentación clínica con el laxante por contacto. Med. españ. (Valencia) 36:372-376 (Nov.)
1958. 64. Schaal, W., and Bachor, W.: Erfahrungen mit (4,4'-Diacetoxy-diphenyl)-(pyridyl-2-methan)-einem neuen Kontakt
Med. klin. 48:1072-73, 1953. 65. Schaal, W., und Bachor, W.: Erfahrungen mit (4,4'-Diacetoxy-diphenyl)-(pyridyl-2-
-einem neuen Kontakt-Laxans, Med. klin. 48:1981-82 (Dez. 25) 1953. 66. Scheel, M.: Erfahrungen mit einem neuen
laxativum in einer indischen Praxis, Hippokrates 20:622-623, 1955. 67. Schlegel, B.: Darstellung der Kolonschleimhaut
ilitätsprüfung des Dickdarmes mit Hilfe verschiedener Kontaktlaxantien, Klin. Wchnschr. 32:557-560, 1954. 68. Schmidt
Berger, E.: Geriatrischer Erfahrungsbericht über die Anwendung des Kontaktlaxativums Dulcolax, Wien. med. Wchnr.
(Mar. 29) 1958. 69. Schmidt, L.: Pharmakologie und Toxikologie einer neuen Klasse von Verbindungen mit laxierende
n, Arzneimittel-Forsch. 3:19-23, 1953. 70. Schmidt, L., und Seeger, E.: Die pharmakologische Wirkung synthetische
n in Beziehung zu ihrer chemischen Konstitution, Arzneimittel-Forsch. 6:19-26 (Jan.) 1957. 71. Schoemperlen, C. B.
l (Dulcolax) as a postoperative laxative, Canad. M.A.J. 81:128 (July 15) 1959. 72. Schulte, E., und Thoenelt, K.: Ver
ng der Vorbereitung und Verbesserung der Methodik beim Roentgenkontrastinlauf durch Anwendung eines Kontakt
ns, Med. Welt 1961 63, 1960. 73. Schultz, O. E., und Schnekenburger, J.: Chemische Konstitution und pharmako
Wirkung der Laxantien unter besonderer Berücksichtigung von Verbindungen mit zwei p-oxyphe-nyl-Gruppen an einem
men Kohlenstoffatom. 3., Arch. Pharm., Berl. 291/63:356-361 (July) 1958. 74. Schultz, O. E., und Schnekenburger, J.
ne Konstitution und pharmakologische Wirkung der Laxantien unter besonderer Berücksichtigung von Verbindungen mit
xyphenyl-Gruppen an einem gemeinsamen Kohlenstoffatom. 4., Arch. Pharm., Berl. 291/63:362-367 (July) 1958. 75
ohn E. S.: A new laxative, Practitioner 177:619 (Nov.) 1956. 76. Sokolow, Jack: Preliminary report on the clinical use of
xative, Clin. Med. 5:1105-06, 1958 (Sept.) 1958. 77. Sowerbutts, J. G.: Hazards of water enemas (Letter to the Editor)
1079:944 (May 2) 1959. 78. Stahel, R., und Kym, O.: Erfahrungen mit R1645, Praxis 47:219-222 (Feb. 27) 1958
pff, F.: Ueber die Behandlung der Obstipation von Hypertonikern die mit Ganglienblockern behandelt wurden, Ther
1, Bern 15:10, 1958. 80. Stasny, R.: Die Behandlung der chronischen Obstipation im Alter, Wien. med. Wchnschr
718, 1957. 81. Stockmeier, Fritz: Erste Erfahrungen mit einem neuen Kontaktlaxativum, München. med. Wchnschr
60, 1953. 82. Vieth, Herbert: Klinische Erfahrungen in der Heilstättenbehandlung der Lungen-Tbc mit einem neuen
axativum, Ther. D. Gegenw. 44:60-62, 1955. 83. Wayand, E., and Schwanzer, H.: Erfahrungsbericht ueber die Ver
t des Kontaktlaxativums La 96a bei abdominal-chirurgischen Patienten, Klin. med. 16:295-296, 1957. 84. Weihs, E.: Kli
eobachtungen und Erfahrungen bei der Behandlung der Obstipation in der Psychiatrie unter Anwendung eines neuer
laxativums ("Laxans Thomae"), Fortsch. Med. 76:27-28, 1958. 85. Weiss, Jerome: Constipation; newer trends in treat
m. J. Proct. 11:111-121 (Apr.) 1960. 86. Zettel, G.: Die Darmentkangung als vorbereitende Massnahme f. Röntgenuntersuch
h des Abdomens, Ther. Gegenw. 96:337-338 (Sept.) 1957. 87. Zitzmann, M.: Unsere Erfahrungen mit der Curare-Lachgas
bei gynaekologischen Operationen, Aerzt. Wchnschr. 9:540-544, 1954. 88. Zimmermann, H.: Die Verwendung von Kon

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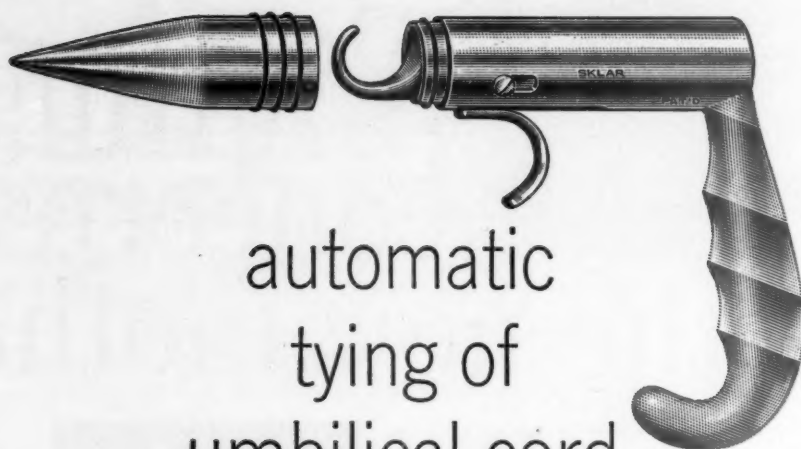
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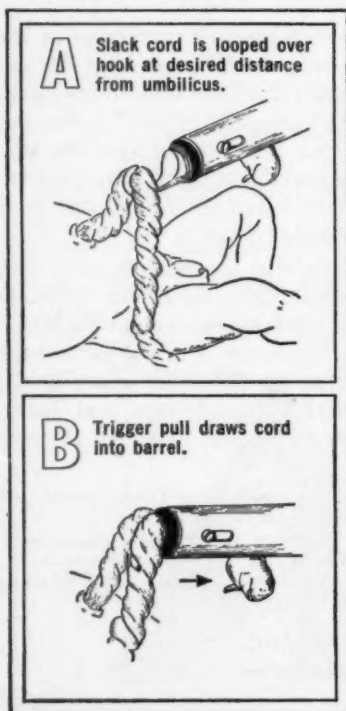
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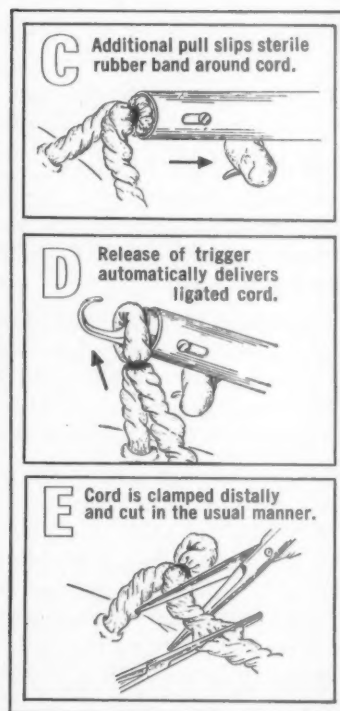
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1. Gravlee, L. C., and Jones, W. N.: Obst. & Gynec. 15:43 (Jan.) 1960. * U. S. PAT. NO. 2,942,604.



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References:

1. Bennett, E. T., and McCann, E. C.: J. Maine
M. A. 45:225. 2. Eichner, E., et al.: Obst. &
Gynec. 6:511. 3. Nulsen, R. O., et al.: Am. J.
Obst. & Gynec. 65:1048.

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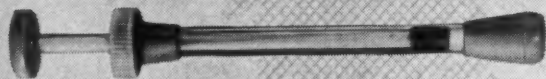
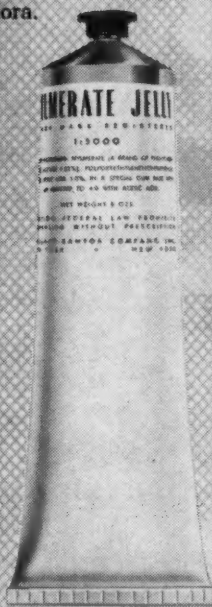
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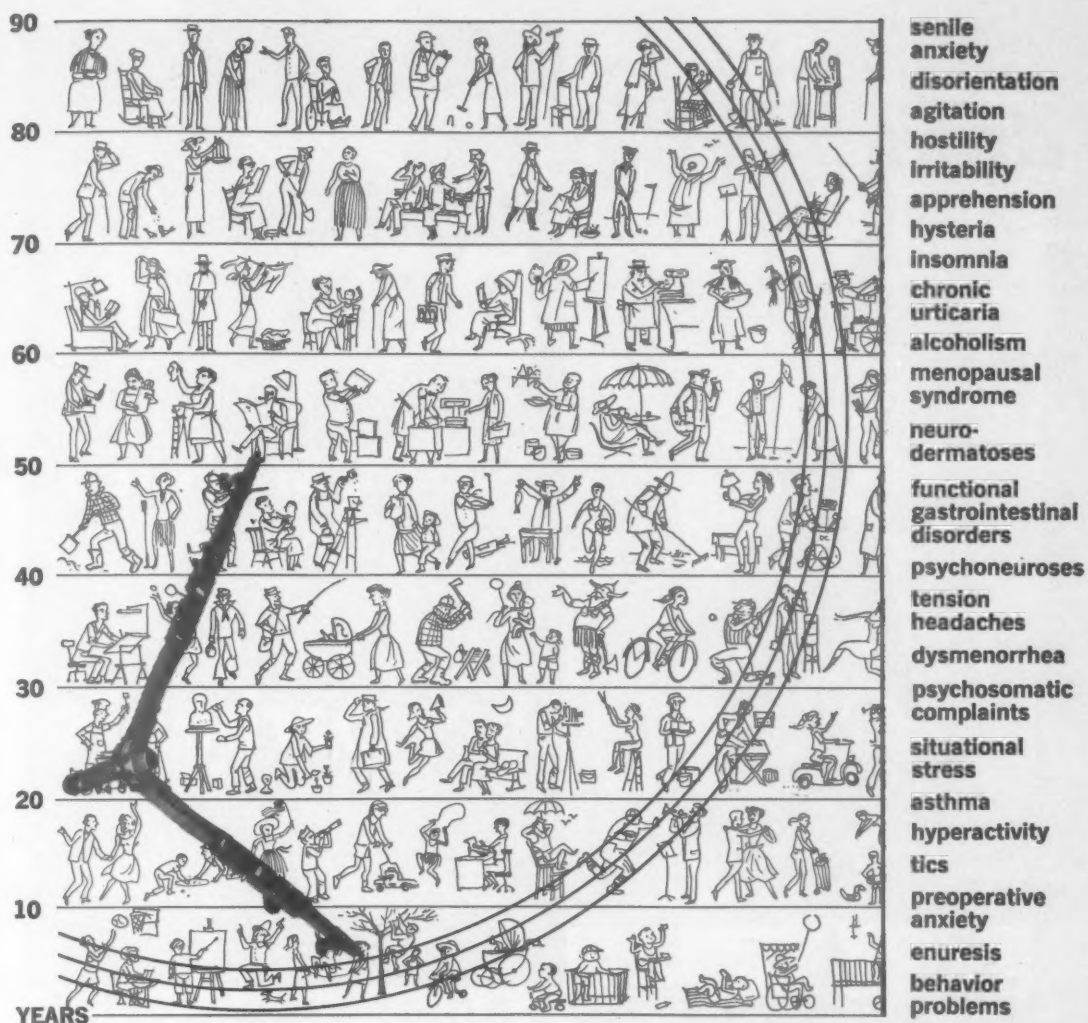
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megaloblastic anemias of pregnancy.



LEDERLE LABORATORIES
A Division of
AMERICAN CYANAMID COMPANY
Pearl River, New York



CONSISTENTLY GOOD
CLINICAL RESULTS
IN TRICHOMONAL
AND MONILIAL VAGINITIS

TRICOFURON IMPROVED (Suppositories and Powder)
cured 143 of 161 patients with vaginitis due to
Trichomonas vaginalis, *Candida* (*Monilia*) *albicans*,
or both. "Almost immediate symptomatic
improvement was noted with the first insufflation."

Criteria for cure: freedom from
infecting organisms as well as symptoms on
repeated examinations during a three-month follow-up.
This cure rate of 88.8% is "surprisingly similar"
to results reported by earlier investigators.

Coolidge, C. W.; Glisson, C. S., and Smith, A. S.:
J.M.A. Georgia 48:167, 1959.

TRICOFURON®
IMPROVED

2-step treatment brings swift relief,
eradicates stubborn trichomonads,
Candida (*Monilia*) *albicans*,
Hemophilus vaginalis

1. **POWDER** for weekly insufflation in your office.
MICOFUR®, brand of nifuroxime, 0.5%
and FUROXONE®, brand of furazolidone, 0.1% in
an acidic water-dispersible base.

2. **SUPPOSITORIES** for continued home use
—1st week one suppository in the morning
and one on retiring. After 1st week, one
suppository at night may suffice.

Continue use of suppositories during menses.
Treatment should be continued throughout a complete
menstrual cycle and for several days thereafter.

MICOFUR 0.375% and FUROXONE 0.25%
in a water-miscible base.

*Rx new box of 24 suppositories with applicator
for more practical and economical therapy.*

*Also available:
box of 12 suppositories with applicator.*

NITROFURANS—a unique class of antimicrobials
EATON LABORATORIES, NORWICH, NEW YORK

for the silent syndrome*...

**the unmentioned edema, mood changes,
GI distress, preceding menstruation*

a comprehensive therapy

NEW
 **CYCLEX**[®]
HYDRODIURIL[®] WITH MEPROBAMATE
HYDROCHLOROTHIAZIDE

to relieve the symptoms

for EDEMA...

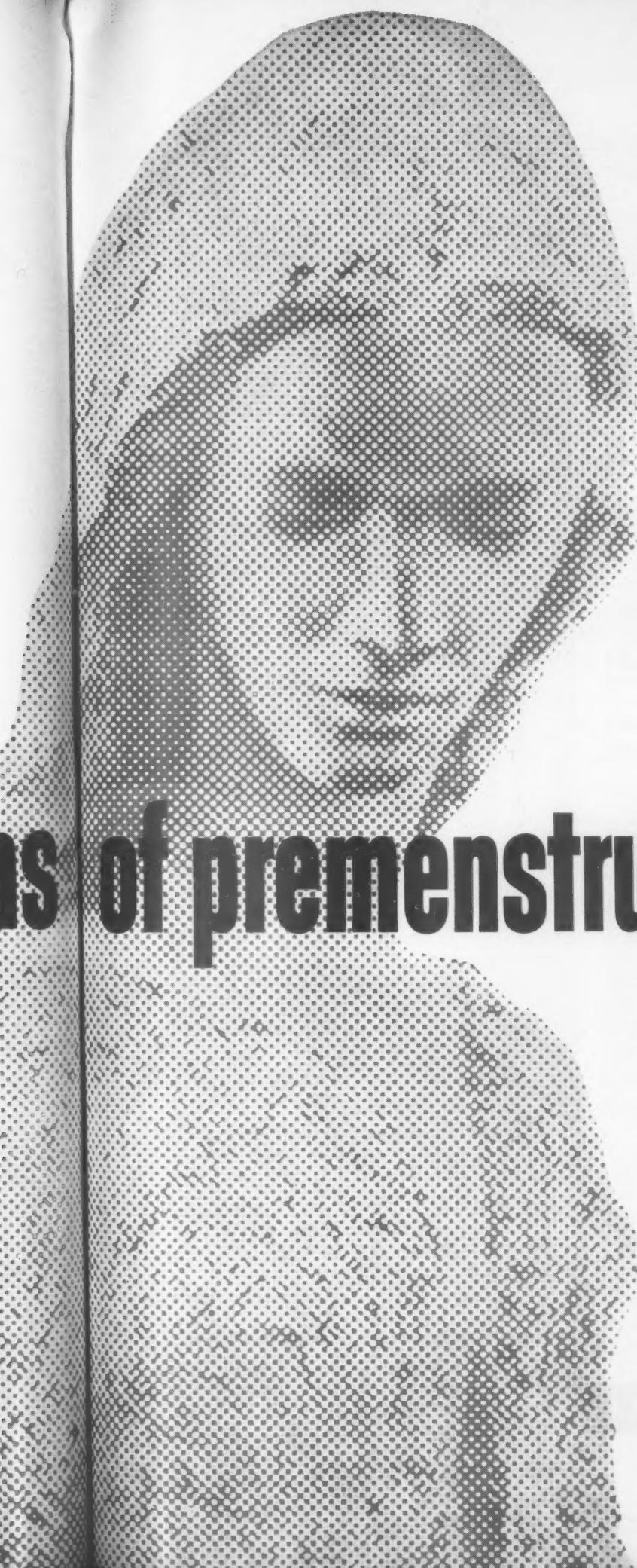
CYCLEX provides the prompt
diuresis of HYDRODIURIL
for rapid reduction of
weight gain, breast fullness,
abdominal congestion

for MOOD-CHANGES...

CYCLEX supplies the effective
relief of meprobamate for nerv-
ousness, irritability, tension,
nausea, malaise, insomnia

for GI DISTRESS...

CYCLEX affords quick-acting
relief of nausea and
bloating associated with
premenstrual tension.



INDICATION: CYCLEX is indicated for the relief of premenstrual tension with edema.

USUAL DOSAGE:

One CYCLEX Tablet 1 or 2 times daily, beginning when symptoms appear and continuing until the onset of menses.

s of premenstrual tension

SUPPLIED: CYCLEX Tablets are supplied in bottles of 100. Each tablet contains 25 mg. of hydrochlorothiazide and 200 mg. of meprobamate.

Additional information on CYCLEX is available to physicians on request.

CYCLEX and HYDRODIURIL are trademarks of Merck & Co., INC.



MERCK SHARP & DOHME
Division of Merck & Co., INC.
West Point, Pa.

IN ALL TYPES OF VAGINITIS



THE FLORAQUIN[®] REGIMEN

Reverses Vaginal Pathology Toward Normal Physiology—

Basically the Floraquin regimen accomplishes the following three-step restorative action:

Step 1—**Diodoquin**[®] content destroys monilia, protozoa and trichomonads, thereby clearing the way for ...

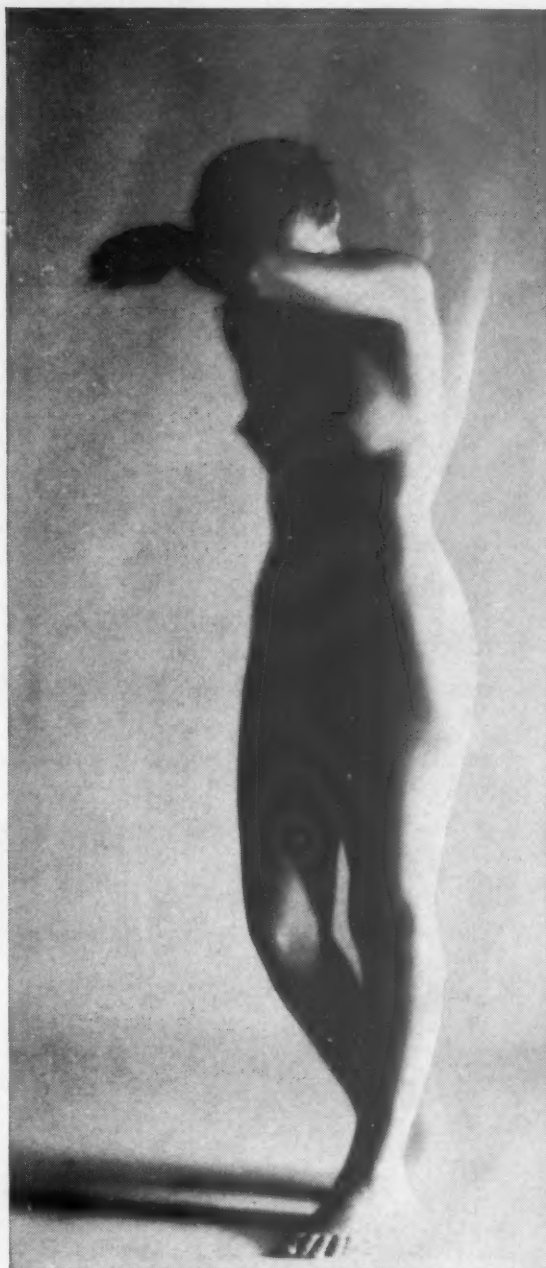
Step 2—**Acid** content helps reestablish the normal pH (3.8 to 4.4) favorable to the regrowth of Döderlein bacilli.

Step 3—**Dextrose** and **lactose** content furnishes essential nutriment to Döderlein bacilli.

Treatment Procedure—Following an initial three to five-day office treatment, the patient is "... issued a prescription for Floraquin vaginal suppositories which she is instructed to insert high into the vagina each evening. On the morning following each application of these suppositories, the patient should take a vinegar water douche. ... The treatment continues through the next menstrual period, both the douches and the insertion of the suppositories being continued through the menstrual period."*

Intravaginal Applicator for Simplified Self-Treatment

With this smooth, unbreakable, plastic plunger the tablets may be placed in the vaginal fornices, assuring coating of the entire mucosa as the tablets disintegrate. A Floraquin applicator is supplied with each box of 50 tablets.



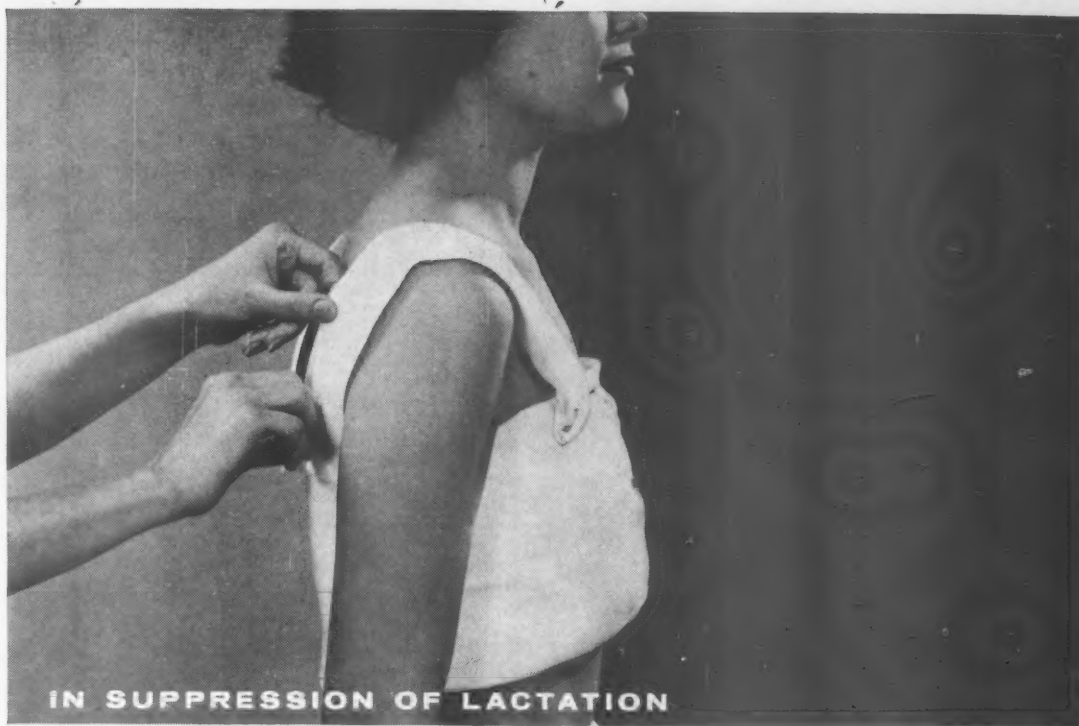
Supplied: Powder — bottles of 1 and 8 ounces.
Vaginal tablets—boxes of 24 and also boxes of 50 with applicator.

G. D. Searle & Co., Chicago 80, Illinois.

*Williamson, P.: Trichomonad Infestation, M. Times 84:929 (Sept.) 1956.

SEARLE

Research in the Service of Medicine



IN SUPPRESSION OF LACTATION

Vallestril[®]

provides notable purity of action—
singularly free from
withdrawal bleeding, nausea or
secondary engorgement

The high degree of clinical satisfaction which Vallestril provides in suppressing postpartum engorgement and lactation derives from its distinctive pharmacologic properties. Unlike other estrogenic agents, Vallestril is neither a steroid nor a derivative of stilbestrol. Since it is structurally unique, Vallestril is capable of producing a unique pattern of therapeutic effects.

This pattern combines a high order of estrogenic activity with a notably low incidence of withdrawal bleeding, drug-induced nausea or rebound engorgement of the breasts. Moreover, Vallestril does not inhibit normal postpartum involution of the uterus.

These benefits have been reliably assessed. The Council on Drugs of the American Medical Association states: "Methallenestril causes fewer gastrointestinal upsets than does diethylstilbestrol." Schneeberg and his associates report that the "slight bleeding" re-

corded in a study of 198 patients was "probably of no significance and was doubtless no more than would have occurred in these individuals without therapy." And Shook found that Vallestril successfully prevents breast symptoms and lactation and "is not followed by secondary lactation and breast engorgement, does not result in withdrawal bleeding and does not inhibit normal involution of the uterus."

The recommended dosage of Vallestril, brand of methallenestril, for suppression of lactation is 40 mg. daily for five days, beginning as soon after delivery as practical. Vallestril is supplied as uncoated, unscored tablets of 20 mg.—also as uncoated, scored tablets of 3 mg.

G. D. SEARLE & CO.
CHICAGO 80, ILLINOIS

Research in the Service of Medicine

References available on request.

BAMADEX A logical combination for appetite suppression

meprobamate plus d-amphetamine... suppresses appetite... elevates mood... reduces tension... without insomnia, overstimulation or barbiturate hangover.

meprobamate 400 mg., with d-amphetamine sulfate 5 mg., Tablets

anorectic-ataractic

Dosage: One tablet one-half to one hour before each meal.

Lederle

On to the job

Blood Services

IN BRIEF

Vistaril® HYDROXYZINE HYDROCHLORIDE Parenteral Solution

Vistaril is a rapid-acting calmative with a wide margin of safety. Its prepartum use generally permits a reduction in dosage of narcotics and barbiturates. Vistaril's antiemetic properties further enhance its pre- and postpartum usefulness.

ACTIONS & INDICATIONS: Vistaril, as part of a prepartum regimen, can safely relax your patients by allaying fear and apprehension.

ADVANTAGES: Vistaril produces a calming effect without hypnosis. Vistaril provides direct and secondary muscle relaxation. Vistaril apparently is non-addicting—discontinuance after months of treatment has not produced withdrawal symptoms. Vistaril has a remarkable record of safety, when used in recommended dosage. Unlike the phenothiazines, parkinsonism and blood or liver toxicities have not been reported with Vistaril. Unlike the rauwolfia derivatives, Vistaril acts rapidly, does not increase gastric secretions, and there have been no reports of nasal congestion, drug-induced depression, or sinusitis associated with its use. Unlike the meprobamates, there have been no reports of incoordination, ataxia, abdominal discomfort, anorexia, nausea, vomiting, diarrhea, allergic dermatitis, or anaphylactic reactions. VISTARIL PARENTERAL SOLUTION permits rapid action and may be given via I.M. or I.V. routes.

CONTRAINDICATIONS: There are no known contraindications to Vistaril.

SIDE EFFECTS AND PRECAUTIONS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing upon reduction of dosage or within a few days of continued therapy. Dryness of mouth may be encountered at higher dosages. The potentiating action of hydroxyzine must be taken into consideration when it is used in conjunction with C.N.S. depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is for 24-48 hours, unless changed by judgment of physician.

ADMINISTRATION AND DOSAGE: Vistaril dosage varies with the state and response of each patient, rather than on a weight basis. Dosage should be individualized by the physician for optimum results. The usual parenteral dosage in prepartum sedation is 25-50 mg. I.M. or I.V. q. 4 h., p.r.n., (alone or in conjunction with reduced dosages of narcotics).

HOW SUPPLIED: Vistaril Parenteral Solution—10 cc. vials and 2 cc. Steraject® Cartridges, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc. Vistaril Capsules (as the pamoate)—25, 50, and 100 mg. Oral Suspension (as the pamoate)—25 mg. per 5 cc. teaspoonful.

More detailed professional information available on request.

PFIZER LABORATORIES
Division, Chas. Pfizer & Co., Inc.
Brooklyn 6, N. Y.

They can be separated

**COMFORTABLE
PREPARTUM
SEDATION**

**FREQUENT
RESPIRATORY
DEPRESSION
AND HYPOTENSION**

VISTARIL PARENTERAL SOLUTION (used either I.M. or I.V.) helps to achieve desired prepartum sedation while virtually eliminating undesirable reactions. The adjunctive use of hydroxyzine may materially reduce the amount of narcotic required for satisfactory analgesia, thus maintaining comfort for the mother while minimizing respiratory distress of the neonate. VISTARIL also effectively allays pre- and postpartum tensions and anxieties of the mother, and is valuable for its control of nausea and vomiting.

Vistaril®
HYDROXYZINE HYDROCHLORIDE

Parenteral Solution

Pfizer Science for the world's well-being™

A
logical
prescription for
overweight patients

anorectic-ataractic

BAMADEX

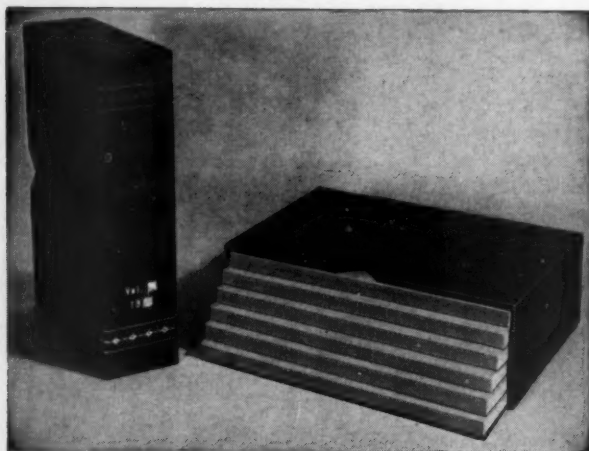
meprobamate 400 mg., with d-amphetamine sulfate 5 mg., Tablets

meprobamate plus d-amphetamine...
depresses appetite...elevates mood...
eases tensions of dieting...without over-
stimulation, insomnia or barbiturate
hangover.

Dosage: One tablet one-half to one hour before each meal.



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with every \$1 package you send
to the world's hungry thru the
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IN A WIDE RANGE OF
COMMON SKIN DISORDERS

NEW FURACIN[®]-HC (NITROFURAZONE 0.2% AND HYDROCORTISONE 1%, EATON) CREAM

INFECTED AND POTENTIALLY INFECTED DERMATOSES / PYODERMAS / ULCERS
BURNS / AFTER PLASTIC, ANORECTAL AND MINOR SURGERY



FURACIN-HC Cream combines the anti-inflammatory and antipruritic effect of hydrocortisone with the dependable antibacterial action of FURACIN[®], brand of nitrofurazone—the most widely prescribed single topical antibacterial. The broad bactericidal range of FURACIN includes stubborn staphylococcal strains, and there has been no development of significant bacterial resistance after more than a dozen years of widespread clinical use. FURACIN is gentle to tissues, does not retard healing; its low sensitization rate is further minimized by the presence of hydrocortisone.

FURACIN-HC Cream is available in tubes of 5 Gm. and 20 Gm. Fine vanishing cream base, water-soluble.

NITROFURANS—a unique class of antimicrobials / EATON LABORATORIES, NORWICH, NEW YORK
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when surgery or childbirth stops intestinal peristalsis

Ureco

sis

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Chloride

(Bethanechol Chloride)

helps restore normal gastrointestinal function
—without uncomfortable enemas or intubation

Because it stimulates peristalsis, URECHOLINE helps restore normal gastrointestinal function. Given prophylactically soon after surgery or childbirth, or therapeutically when abdominal distention occurs, URECHOLINE facilitates expulsion of gas and promotes evacuation.
Supplied: 5 mg. and 10 mg. tablets, bottles of 100. 1-cc. ampuls containing 5 mg.

For additional information, write Professional Services, Merck Sharp & Dohme, West Point, Pa.



MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., PHILADELPHIA 1, PA.



The Pregnant

- and a natural way to meet her special need for calcium
- with low-calorie Carnation Instant

Drinking enough milk during pregnancy to assure sufficient calcium has posed the problem of unwanted fat calories — till recently.

Now a *natural* way to help assure your patients' good calcium and nutritional status is the excellent new food — *new Carnation Instant Nonfat Dry Milk mixed 25% over-strength.*

One-third cup extra crystals per liquid quart when mixing provides 25% more cal-

cium, protein, and B-vitamins than ordinary nonfat milk. Because your patients can add this additional amount of Carnation Instant Nonfat, they get *needed* nutrition — *without* excessive calories. Its richer, more delicious flavor is a *natural* way to *extra* nutrition they will enjoy. Costs them only 12¢ a quart.



ANOTHER QUALITY PRODUCT OF CARNATION COMPANY, LOS ANGELES 36, CALIFORNIA

In threatened abortion...

Provera* is now available in a new long-acting injectable form:



ACTUAL SIZE

Formula:

Sterile micronized medroxyprogesterone acetate (17-alpha-hydroxy-6-alpha-methylprogesterone acetate).

Supplied:

In 1 cc. and 5 cc. size vials

REFERENCES: 1. Boischann, Hanns-Werner, and Drews, Renate, "The Effect of 6-alpha-methyl-17 alpha-acetoxypregn-4-ene-20-one on the Endometrium," Brook Lodge Symposium, Progesterone, 1960, in press. 2. Wied, George L., and Davis, M. Edward, Brook Lodge Symposium, Progesterone, 1960, in press.

*TRADEMARK, REG. U.S. PAT. OFF.

**TRADEMARK

Depo-Provera**

Potent

Depo-Provera is 4 times as potent as any other available progestogen (by castrate assay).

Long-acting

A single 50 mg. injection of Depo-Provera will produce a progestational effect that lasts for up to 16 days.

Well tolerated

No significant untoward side effects have been reported.

More acceptable to patient

Micronized in sterile aqueous suspension—little or no pain at site of injection.

Depo-Provera

Upjohn

The Upjohn Company, Kalamazoo, Michigan

NOW a truly definitive answer
to an ever-present problem

✿ Tassette® ✿

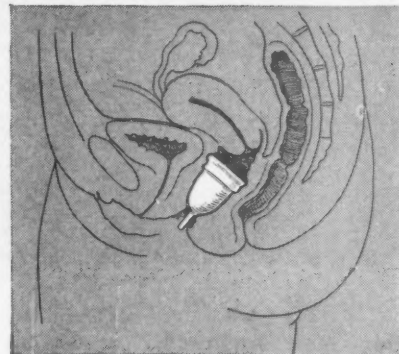
the safe and sanitary
menstrual cup

You can prescribe Tassette with full assurance that your patient will find a safe, effective and completely acceptable answer to her menstrual control problem. *Tassette*, made of soft pliable rubber fits anatomically at the mid point of the vaginal wall and acts as a catch basin for the menstrual flow (see anatomical drawing). It is easily folded, needs no inserter, and can be simply emptied and replaced as needed. Tassette requires no measurements or fitting, and can be worn with complete comfort at all times.

Tassette permits your patient to swim, dance and engage in any activity because it catches the flow and seals it off completely. Thus there is no odor or possibility of leakage or staining as may occur during periods of heavy flow when tampons are used. There is no danger of chafing, irritation or infection, and no belt is required, as with ordinary sanitary napkins.

Tassette has many medical applications other than its use as a menstrual cup. During the intermenstrual period it provides the most satisfactory and safe method for collecting vaginal, cervical or uterine secretions for diagnostic purposes. Tassette has also been used to insure against leakages in vesico-vaginal fistula.

Modern internal menstrual control is now accepted by the medical profession and Tassette is widely recommended by gynecologists in place of sanitary napkins and tampons. In order to acquaint you with Tassette this special offer is made: Send \$3.50 (reg. price \$4.95) for one Tassette with complete directions, postage prepaid. Tassette guarantees satisfactory use for two years or your money back.



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DECLOMYCIN[®]

DEMETHYLCHLORTETRACYCLINE LEDERLE



*attains
sustains
retains*

*extra
antibiotic
activity*

extra-activity...promptly attained

DECLOMYCIN Demethylchlortetracycline attains—usually within two hours—blood levels more than adequate to suppress susceptible pathogens. These levels are attained in tissues and body fluids on daily dosages substantially lower than those required to elicit antibiotic activity of comparable intensity with other tetracyclines. With other tetracyclines, the average, effective, adult daily dose is 1 Gm. With DECLOMYCIN Demethylchlortetracycline, it is only 600 mg.



DECLOMYCIN

evenly sustained long retained

DECLOMYCIN Demethylchlortetracycline sustains, through the entire therapeutic course, the high activity levels needed to control the primary infective process and to check the onset of a complicating secondary infection at the original—or at another—site. This combined therapeutic action is sustained, in most instances, without the pronounced hour-to-hour, dose-to-dose, peak-and-valley fluctuations in activity levels which characterize other tetracyclines.

DECLOMYCIN Demethylchlortetracycline retains significant activity levels, up to 48 hours after the last dose is given. At least a full, extra day of positive antibacterial action may thus be confidently expected. One capsule four times a day, for the average adult in the average infection, is the same as with other tetracyclines—but the **total** dosage is lower and the duration of anti-infective action is longer.

DECLOMYCIN—SUSTAINED ACTIVITY LEVELS

OTHER TETRACYCLINES—PEAKS AND VALLEYS

PROTECTION AGAINST PROBLEM PATHOGENS

1

DAYS 1 2 3 4 5 6

DAYS OF TETRACYCLINE A¹ DOSAGE

DURATION OF PROTECTION

DAYS OF TETRACYCLINE B² DOSAGE

DURATION OF PROTECTION

DAYS OF TETRACYCLINE C³ DOSAGE

DURATION OF PROTECTION

DAYS OF DECLOMYCIN DOSAGE

DURATION OF PROTECTION

(1) Oxytetracycline. (2) Chlortetracycline. (3) Tetracycline.

PROTECTION AGAINST RECURRENCE

DECLOMYCIN[®]

DEMETHYLCHLORTETRACYCLINE LEDERLE

- higher activity/intake ratio—positive antibacterial action
- sustained activity levels—protection against problem pathogens
- up to two extra days' activity—protection against recurrence

CAPSULES, 150 mg., bottles of 16 and 100. **Dosage:** Average infections—1 capsule four times daily. Severe infections—Initial dose of 2 capsules, then 1 capsule every six hours.

PEDIATRIC DROPS, 60 mg./cc. in 10 cc. bottle with calibrated, plastic dropper.

Dosage: 1 to 2 drops (3 to 6 mg.) per pound body weight per day—divided into 4 doses.

SYRUP, 75 mg./5 cc. teaspoonful (cherry-flavored), bottles of 2 and 16 fl. oz.

Dosage: 3 to 6 mg. per pound body weight per day—divided into 4 doses.

for the
added measure
of protection
in clinical
practice

PRECAUTIONS: As with other antibiotics, DECLOMYCIN may occasionally give rise to glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis or dermatitis. A photodynamic reaction to sunlight has been observed in a few patients on DECLOMYCIN. Although reversible by discontinuing therapy, patients should avoid exposure to intense sunlight. If adverse reaction or idiosyncrasy occurs, discontinue medication.

Overgrowth of nonsusceptible organisms is a possibility with DECLOMYCIN, as with other antibiotics. The patient should be kept under observation.

DECLOMYCIN[®]

DEMETHYLCHLORTETRACYCLINE LEDERLE

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

**Helps you
take the misery out of menopause**
as hormones alone often don't do



**Fast-acting Milprem directly relieves
both emotional dread and estrogen deficiency**

Dosage: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

Composition: Miltown (meprobamate) + conjugated estrogens (equine).

Supplied: **Milprem-400**, each coated pink tablet contains 400 mg. Miltown and 0.4 mg. conjugated estrogens (equine). **Milprem-200**, each coated old-rose tablet contains 200 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Both potencies in bottles of 60.

Literature and samples on request.

Many physicians find that estrogen therapy is not enough for the woman who is also filled with anxiety by her menopause. Her emotional dread may make her so miserable that it becomes a real clinical problem.

This is where Milprem helps you so much. It calms the woman's anxiety and tension; prevents moody ups and downs; relieves her insomnia and headache. At the same time, it checks hot flushes by replacing lost estrogens. The patient feels better than she did on estrogen therapy alone. And your counsel and your assurances can now help her make her adjustment much faster.

Milprem[®]

(Miltown[®] plus natural estrogens)

ENP-1302

 **WALLACE LABORATORIES/Cranbury, N. J.**

Menopausal Patients are Pleased with **ESTROSED®** Therapy

Estrogenic deficiencies and emotional disturbances are successfully managed with flexible, potent Estrosed

- Vasomotor instabilities respond to ethinyl estradiol, "... one of the most potent estrogens known."¹
- Nervousness and insomnia are quieted with reserpine, "... useful chiefly for its psychotherapeutic sedative action in the symptomatic management of patients with anxiety or tension psychoneurosis ..."²

Your results with Estrosed therapy will be gratifying. Estrosed contains 0.01 mg. ethinyl estradiol and 0.1 mg. reserpine.

Low Dosage—Economical Therapy

Suggested dosage: One tablet three times daily until symptoms are controlled. Thereafter reduce to maintenance dosage of one tablet every day or two, as may be required.

1. N.N.R., 1959, 515; 2. Ibid., 376

CHICAGO PHARMACAL CO.

5547 N. Ravenswood Ave., Chicago 40, Illinois



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Chicago 40, Ill.

Gentlemen: Please forward generous supply of Estrosed ☐
Literature ☐

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A new concept

STOP ITCHING HELP SKIN RESIST IRRITATION LIDA-MANTLE^{T.M.}

• *Relieves itching and topical pain within minutes . . . "superior to any existing local anesthetic."*¹

• *Not a 'caine' or a 'quinoline'. Virtually non-irritating, non-allergenic, non-toxic . . . over a million uses without a single verified case of sensitization.*²

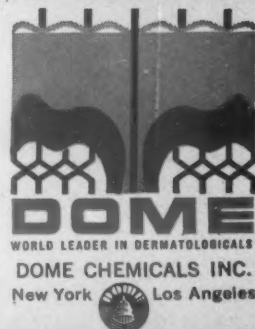
• *The exclusive ACID MANTLE vehicle soothes sensitive skin, speeds healing and wards off recurrences by rebuilding the protective barrier of acidity that helps skin resist inflammation, irritation and infection.*

Available as Creme in ½ oz. and 1 oz. tubes.

3% Xyllocaine* HCl (brand of lidocaine hydrochloride) in the exclusive ACID MANTLE† vehicle.

*Reg. T.M. Astra Pharmaceutical Products, Inc. U.S. Pat. No. 2,441,498. †Reg. T.M. Dome Chemicals Inc.

1. Crawford, O. B.: Anesthesiology 14:278, 1953. 2. Wiedling, S.: Xyllocaine, The Pharmacological Basis For its Clinical Use, Stockholm, Almquist and Wiknell, 1959.



In hysterosalpingography "Ethiodol is the drug of choice, both from a diagnostic and a therapeutic point of view"¹

In a recent clinical study, the marked increase in pregnancy success rate demonstrates "the therapeutic superiority of Ethiodol hysterosalpingography over hysterosalpingography with other radiopaque media or carbon dioxide insufflation in the treatment of infertility."²

Ethiodol is preferred because... "It is an ideal radiopaque medium for hysterosalpingography. Because of its much lower viscosity it is preferable to... any other oily radiopaque medium. X-ray films with Ethiodol give... much better defined contrast than with any of the aqueous, acacia, or other water soluble media."²



Ethiodol®


brand of ethiodized oil, is the ethyl ester of the iodized fatty acids of poppy seed oil, containing 37% iodine. It is available in 10 cc. ampules, boxes of two. A development of Guerbet Laboratories.

Bibliography: 1. Finegold, Wilfred J.: *Internat. J. of Fertil.* 3:143 1958
2. Palmer, A.: *Internat. J. of Fertil.* 4:365 1959



FOUGERA

E. Fougere & Company, Inc., Hicksville, Long Island, N. Y.



*your
episiotomy
patient is
entitled to*

VARIDASE[®]

STREPTOKINASE-STREPTODORNASE LEDERLE

buccal tablets

*for a faster
recovery
with
more
comfort*

Inflammation, swelling, and pain are reduced more rapidly when VARIDASE is added to your post-partum regimen. Your patient has a more comfortable convalescence and a faster return to normal activity.

Precautions: VARIDASE has no adverse effect on normal blood clotting. Care should be taken in patients on anti-coagulants or with a deficient coagulation mechanism. When infection is present, VARIDASE Buccal Tablets should be given in conjunction with antibiotics.

Dosage: One buccal tablet four times daily usually for five days. To facilitate absorption, patient should delay swallowing saliva.

Supplied: Each tablet contains 10,000 Units Streptokinase, 2,500 Units Streptodornase. Boxes of 24 and 100 Tablets.

LEDERLE LABORATORIES, a Division of AMERICAN CYANAMID COMPANY, Pearl River, New York



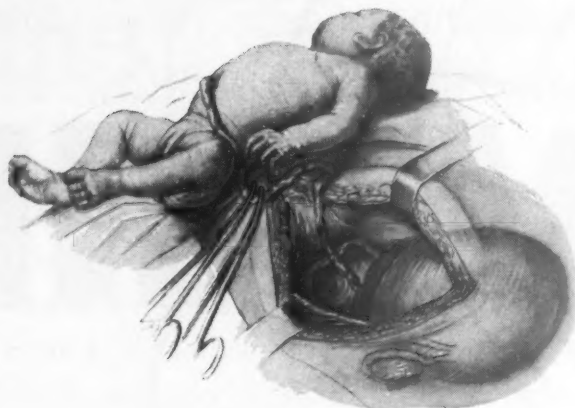
Over 100 step-by-step illustrations like these



*make this new atlas
a lifetime investment
for any physician
practicing obstetrics*

Willson

ATLAS OF OBSTETRIC TECHNIC



This new atlas can be of valuable assistance to any physician practicing obstetrics as a ready reference on technics for normal delivery and on the management of complications which may arise during late pregnancy or labor. Authoritatively written by the eminent obstetrician, J. Robert Willson, M.D., and beautifully illustrated with original drawings by one of the nation's foremost medical artists, Miss Daisy Stillwell, this definitive work covers all the maneuvers which may be necessary to complete delivery at or near term. The illustrations above, reduced to approximately 50% of the actual size as they appear in the book, are just two of more than 100 which are included in this atlas on some 56 full page plates. Each plate is accompanied by an appropriate descriptive legend on a facing page.

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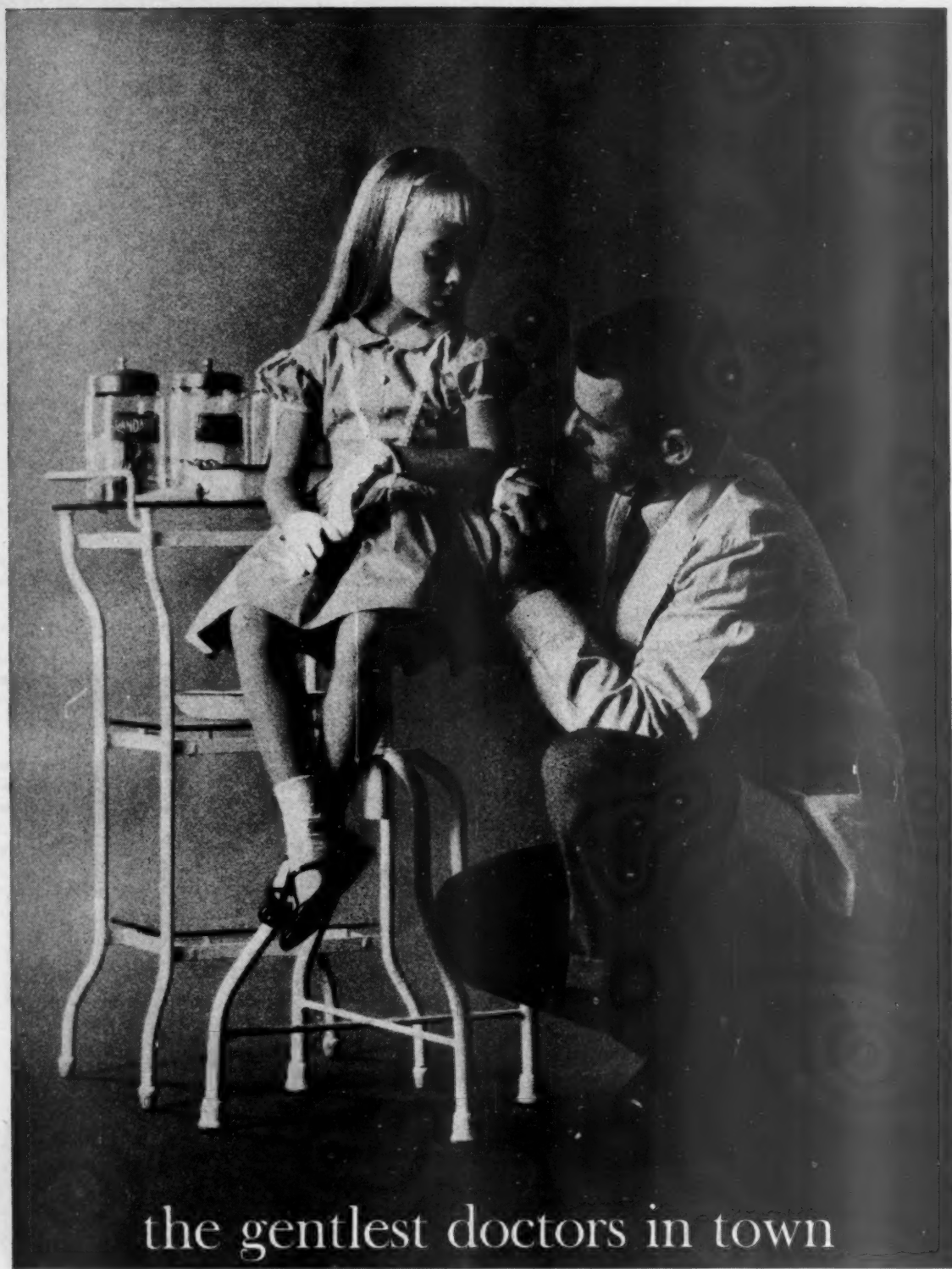
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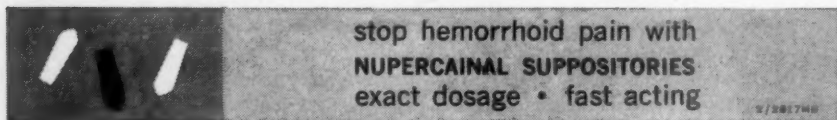
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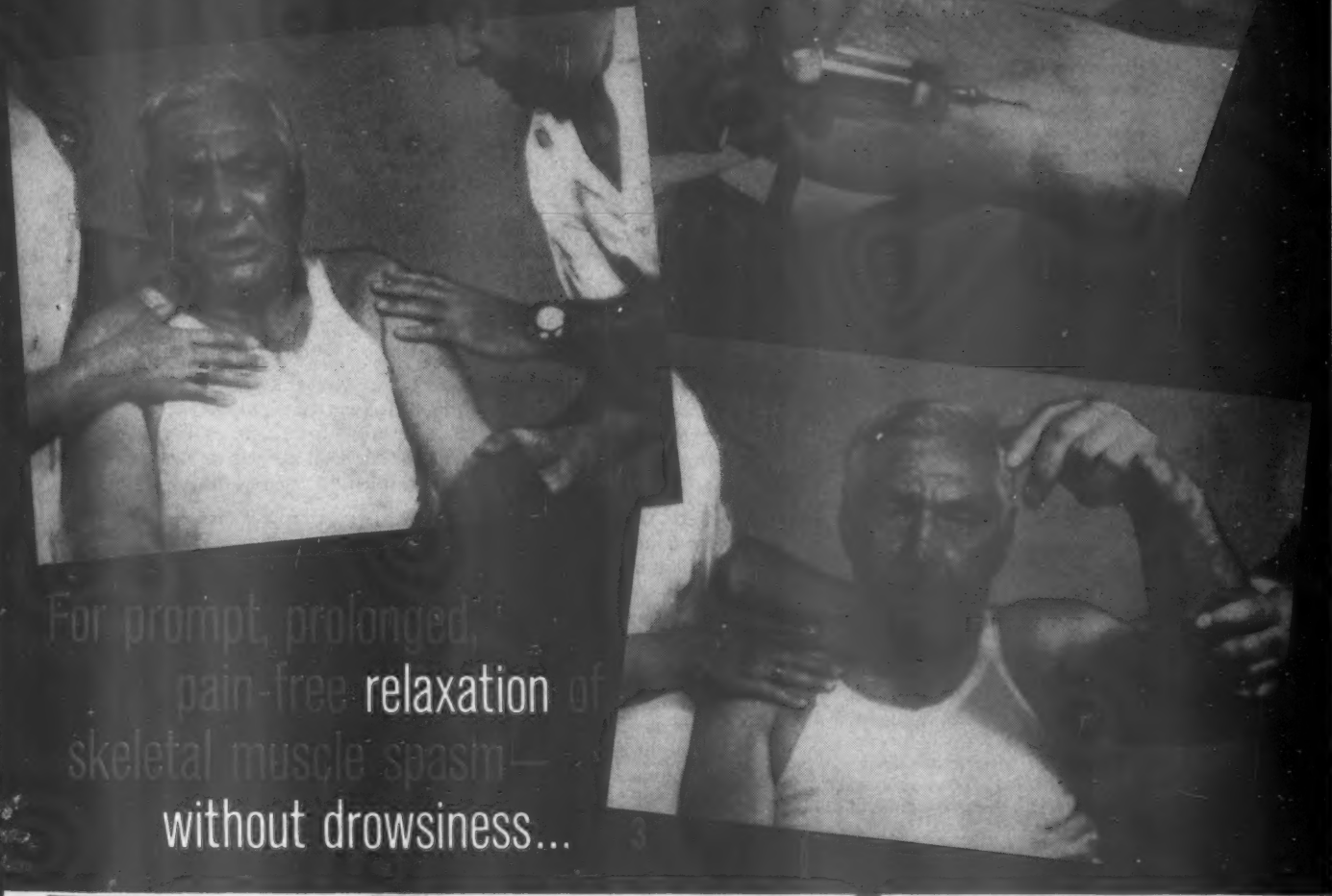
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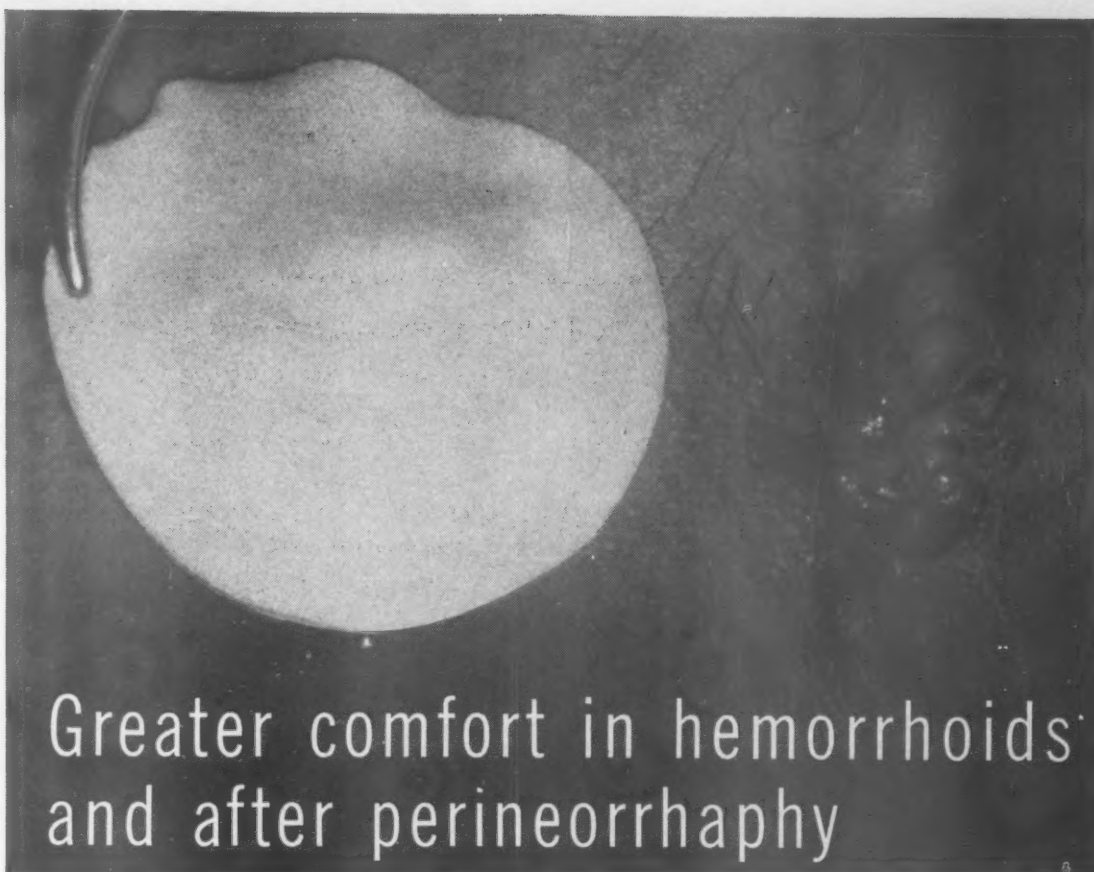
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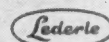
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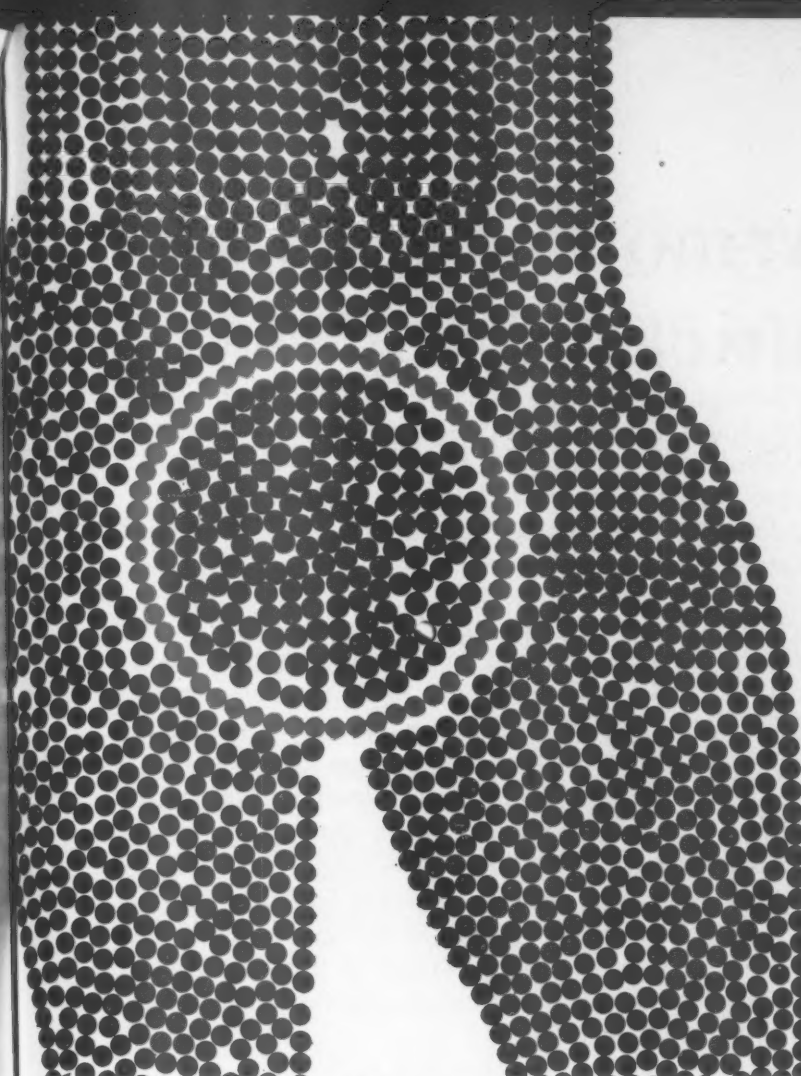
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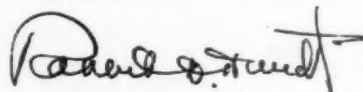
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Adrenosem The S. E. Massengill Com- pany 17, 18	Enfamil Mead Johnson & Company -- 36	Pitocin Parke, Davis & Company 25
Agoral Warner-Chilcott 19	Es-A-Cort Dome Chemicals Inc. 97	PMB 200 Ayerst Laboratories 149
Americaine Arnar-Stone Laboratories, Inc. 13	Estrosed Chicago Pharmacal Co. 134	Pramilets Abbott Laboratories 44, 45
Amsco Surgical Chair American Sterilizer 29	Ethiodol E. Fougere & Company, Inc. 136	Precalcins Walker Laboratories, Inc. 154
Atarax J. B. Roerig & Company 111	Filibon Lederle Laboratories 114	Premarin Ayerst Laboratories 94
AVC Cures The National Drug Company 139	Floraquin G. D. Searle & Co. 118	Proloid Warner-Chilcott 7
Baby Cereal Gerber Baby Foods...61, 62, 63, 64	Formaldehyde Germicide Bard-Parker Company, Inc. -- 84	Ramases Julius Schmid, Inc. 107
Bamadex Lederle Laboratories 106, 120, 122, 146	Fosfree Mission Pharmacal Co. 106	Rauwiloid Riker Laboratories -- Third Cover
Bendectin The Wm. S. Merrell Company 32, 33	Furacin Cream Eaton Laboratories 152	Ritalin Ciba Pharmaceutical Products 78, 79
Bonadoxin J. B. Roerig & Company 59	Furacin-HC Cream Eaton Laboratories 123	Robaxin A. H. Robins Co., Inc. 141
Bonine Pfizer Laboratories 65	Furadantin Eaton Laboratories 56, 57	Senokot The Purdee Frederick Company 9
Carnation Instant Nonfat Dry Milk Carnation Company 126	Gelusil Warner-Chilcott 75	Similac Ross Laboratories 96
Chymoral Armour Pharmaceutical Com- pany 148	Gentia-Jel Westwood Pharmaceuticals... 27, 28	Soma Wallace Laboratories 143
Combidi Spansule Smith Kline & French 100	Gravlee Gun Sklar 108	Soma Compound Wallace Laboratories 16
Compazine Smith Kline & French 31	Hespiridin Sunkist Growers 99	Stelazine Smith Kline & French 3
Cooper Creme Whittaker Laboratories, Inc. -- 146	HydroDiuril Merck Sharp & Dohme -- 76, 77	Striatran Merck Sharp & Dohme -- 40, 41
Cortisporin Burroughs Wellcome & Co. (U. S. A.) Inc. 102	Hygroton Geigy Pharmaceuticals 20	Tace The Wm. S. Merrell Company 109
Cyclex Merck Sharp & Dohme -- 116, 117	Kantrex Bristol Laboratories 14	Tampax Tampax Incorporated 12
Cytran The Upjohn Company 80, 81	Kanulase Smith-Dorsey 15	Tassette Tassette, Inc. 128
Darvon Compound Eli Lilly and Company 82	Koromex Compact Holland-Rantos Co., Inc. 10	Tenuate The Wm. S. Merrell Company 53
Declomycin Lederle Laboratories 129, 130, 131, 132	Leritine Merck Sharp & Dohme Fourth Cover	Thiosulfil Ayerst Laboratories 37, 38
Declostatin Lederle Laboratories 90	Librium Roche Laboratories Second Cover	Titralac Riker Laboratories 105
Demerol Winthrop Laboratories 39	Lida-Mantle Dome Chemicals Inc. 135	Tigan Roche Laboratories 42, 43
Depo-Provera The Upjohn Company 127	Livitamin The S. E. Massengill Com- pany 73, 74	Trancoprin Winthrop Laboratories 34, 35
Deprol Wallace Laboratories 113	Lubafax Burroughs Wellcome & Co. (U. S. A.) Inc. 92	Trib Roche Laboratories 147
Desbutal Gradumet Abbott Laboratories 85, 87, 89, 91, 93	Meprospan Wallace Laboratories 5	Trichotine The Fesler Company, Inc. 24
Desitin Suppositories Desitin Chemical Company -- 112	Metrecal Mead Johnson & Company 22, 23	Tricofuron Eaton Laboratories 115
Diaphragms Ortho Pharmaceutical Corpo- ration 26	Milprem Wallace Laboratories 133	Tucks Fuller Pharmaceutical Co. 145
Donnazyme A. H. Robins Company, In- corporated 11	Miltown Wallace Laboratories 54, 55	Urecholine Merck Sharp & Dohme 124, 125
Dorbane Riker Laboratories 21	Modilac Gerber Baby Foods 61, 62, 63, 64	Urised Chicago Pharmacal Company -- 60
Doxidan Lloyd Brothers, Inc. 66	Natalins Mead Johnson & Company -- 67	Vagisec Julius Schmid, Inc. 72
Dramamine G. D. Searle & Co. 83	Norlutin Parke, Davis & Company -- 70, 71	Vallestril G. D. Searle & Co. 119
Dulcolax Geigy Pharmaceuticals 103	Nupercainal Ciba Pharmaceutical Products 140	Vanay Ayerst Laboratories 104
Dyclone Pitman-Moore Company 30	Nylmerate Holland-Rantos Co., Inc. 110	Varidase Lederle Laboratories 137
Edrisal Smith Kline & French 86	Oreticyl Abbott Laboratories 68, 69	Vasodilan Mead Johnson & Company -- 144
Eggs Poultry and Egg National Board 88	Ortho-Gynol Vaginal Jelly Ortho Pharmaceutical Corpora- tion 58	Vistaril Pfizer Laboratories 120, 121
	Ovaltine Ovaltine Food Products --- 46, 47	White Cotton Gowns Teckla 146
		Xylocaine Astra Pharmaceutical Products, Inc. 49, 50, 51, 52

While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

**gas is for balloons...
not for
pregnant
women**



Unlike most prenatal supplements, the PRECALCINS do *not* generate carbon dioxide gas when ingested (see above). Thus, patients experience more comfortable pregnancies—*without* therapy-induced belching, gas pains, or gastric distention. What's more, the PRECALCINS supply more vitamins, minerals, and bioflavonoids than most other one-a-day supplements... and at a low, low cost per day. So give your patients *gas-free* supplementation and make every pregnancy as nutritionally perfect as it is comfortable.

**prescribe the *Precalcins*
for gas-free prenatal nutritional support**

PRECALCIN®: A complete one-capsule-daily vitamin and mineral formula containing calcium and phosphorus (as dicalcium phosphate); bottles of 100, 500 and 1,000. **PRECALCIN® LACTATE:** A complete one-capsule-daily vitamin and mineral formula containing calcium (as lactate) *without* phosphorus; bottles of 100, 500 and 1,000. **PRECALCIN®-D:** A one-dose-daily, two-capsule formulation providing *extra-generous* amounts of calcium (as lactate and phosphate, 1200 mg.); bottles of 60 and 300 pink and blue capsules—the pink capsules containing vitamins and minerals, the blue capsules containing calcium.

WALKER LABORATORIES, INC., MOUNT VERNON, NEW YORK

THE RECOMMENDED DAILY DOSES PRODUCE THIS MUCH GAS—BUT NOT THE PRECALCINS—These balloons dramatically demonstrate the amount of carbon dioxide gas released when the recommended daily doses of six of today's most frequently prescribed prenatal supplements are dropped into simulated gastric juice. The outstanding exception seen here is PRECALCIN which, like PRECALCIN LACTATE and PRECALCIN-D, produces no gas. The reason is simple: All three PRECALCINS contain well-tolerated, *gas-free* sources of calcium—as lactate and/or phosphate—while the other five supplements contain calcium carbonate. When the carbonate salt reacts with gastric juice ($\text{CaCO}_3 + 2\text{HCl} \rightarrow \text{CO}_2 \uparrow + \text{CaCl}_2 \downarrow + \text{H}_2\text{O}$), carbon dioxide is liberated—both in the test tube and in the stomach. So avoid such gaseous discomforts of pregnancy. Prescribe the PRECALCINS.

In Hypertension and Anxiety States

just
two
tablets
at bedtime

CONTROL

with MAXIMUM SAFETY

RAUWILOID®

alseroxylon 2 mg.

In Hypertension

Simplicity of control based on negligible incidence of serious side actions, simplicity of dosage, and applicability to a wide range of patients.

In Anxiety States

Rauwiloid is outstanding for its calming, non-soporific sedation in anxiety states...with or without hypertension.

Compatible with other anti-hypertensive medications. Potentiates therapeutic action of more potent agents and permits their use in reduced and better tolerated dosage.

When more potent hypotensive action is needed, prescribe one of these convenient single-tablet combinations

Rauwiloid® + Veriloid®
alseroxylon 1 mg. and alkavervir 3 mg.

or

Rauwiloid® + Hexamethonium
alseroxylon 1 mg. and hexamethonium
chloride dihydrate 250 mg.

Patients with severe hypertension often can be maintained on Rauwiloid alone after desired blood pressure levels are reached with combination medication.



Northridge, California

almost immediate relief for the mother.¹ Satisfactory relief of labor pain was reported by 123 of 147 patients given LERITINE. Most patients promptly went to sleep...were easily aroused...rested quietly between pains. Respiratory depression or hypotension was not observed. Nausea and vomiting were rare. Length of labor was not affected.¹

Barbiturates were unnecessary in most patients. When used, they were effective in half the usual amount.¹

Parenteral use in obstetrics: 50 mg. of LERITINE (2½ times more potent than meperidine), given intramuscularly or subcutaneously and repeated, if necessary, in three or four hours for a total dose of 100 to 200 mg. For rapid action, 10 mg. in dilution intravenously, by slow injection, simultaneously with 40 mg. intramuscularly or subcutaneously.

labor pain

minimal sedation, reduced hazards for the infant.¹ Infants were given high Apgar ratings on respiratory effort, heart rate, muscle tone, reflex irritability, and color. Only one needed NALLINE® (nalorphine) to counteract respiratory depression.¹

Precautions: Respiratory depression due to LERITINE may rarely occur. If it should, it may be reversed by the antagonist NALLINE, thus providing an additional margin of safety. (Consult package circular for comprehensive statement on all precautions.)

Warning: May be habit-forming. Notice: Subject to the Federal Narcotic Law.

Additional information on LERITINE and NALLINE is available to physicians on request.

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1. Wizenberg, M. J., et al. Am. J. Obst. & Gynec. 78:405 (Aug.) 1959.

Leritine*

anileridine
EVEN FOR INTENSE PAIN



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